Chemical Library

MAY 14 1941

SCIENTIFIC EDITION

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

CONTENTS OF THIS ISSUE

Acetanilid Studies. I. Acute Toxicity . . . 91
James C. Munch, Harry J. Pratt and Lilian M. Phillips

Certain Salts of Atropine, Ephedrine, Epinephrine and Procaine 98
Frank M. Goyan and T. C. Daniels

A Study of Intermolecular Compounds . . . 105
Helmut M. Haendler with L. Wait Rising

Report on the Vanadium Oxytrichloride Colorimetric Method for the Determination of Capsaicin in Capsicum 107
Alice Hayden and C. B. Jordan

Pharmaceutical Emulsions. II. A Study of the English Method 114
William J. Husa and Charles H. Becker

Le Clergé et al Pharmacie 115
K. L. Kaufman

Book Reviews 120

Abstracts 97–128

Advertising—Cover Pages 2, 3, 4 and pp. I to X

Published by the American Pharmaceutical Association. Publication office, 20th and Northampton Sts., Easton, Pa. Editorial office: Scientific Edition, 32 S. Greene St., Baltimore, Md. Practical Pharmacy Edition: 2215 Constitution Ave., Washington, D. C.

Annual Subscription: Journal of the American Pharmaceutical Association, complete $5.00; Canada, $6.00; Other Foreign, $6.50. (*a*) Scientific Edition, $4.00; Canada, $4.35; Other Foreign, $4.50; Single Numbers, $0.35; Canada, $0.40; Other Foreign, $0.50. (*b*) Practical Pharmacy Edition, $1.50; Canada, $1.80; Other Foreign, $2.00; Single Numbers, $0.15; Canada, $0.20; Other Foreign, $0.25.

No claims will be allowed for Journals lost in the mails due to: Failure to notify of change of address (thirty days' notice required); after a lapse of three months; failure to receive wrappers from returned Journals.

Entered as second-class matter January 23, 1917, at the Post Office at Easton, Pa., under the act of March 3, 1879, as 24 times a year: Scientific Edition monthly on the fifth. Practical Pharmacy Edition monthly on the 20th. Acceptance for mailing at a special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized July 10, 1918.

Vol. XXX, No. 4 APRIL, 1941

PEPSENCIA with VITAMIN B_1

(thiamine hydrochloride)

PEPSENCIA with VITAMIN B_1 is a new standardized product. Each fluid ounce contains 1000 International units of vitamin B_1.

Put up only in 8 ounce bottles.

Trade Price $12 a dozen.

Literature sent on request

FAIRCHILD BROS. & FOSTER

New York, New York

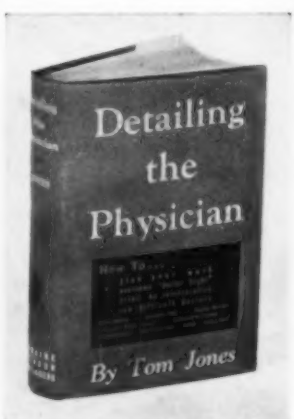
USEFUL BOOKS FOR THE PHARMACIST

DETAILING THE PHYSICIAN

by Tom Jones

INCREASE YOUR SALES!

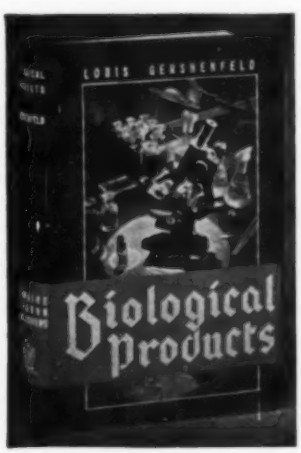
This single volume contains proven methods of productive detailing as practiced by nationally known manufacturers. An indispensable working tool for detail men, sales and advertising managers, pharmacists and surgical dealers.



$2.75

BIOLOGICAL PRODUCTS

by Dr. Louis Gershenfeld



290 Pages

40 Illustrations

The first accurate, concise volume of complete information regarding the Biological Products. Indispensable for the physician, bacteriologist and public health worker.

$4

Send me .....BIOLOGICAL PRODUCTS

.....DETAILING THE PHYSICIAN OR BOTH

Enclosed check for $.....

ROMAINE PIERSON PUBLISHERS, INC.

95 Nassau St. New York, N. Y.

Name.....

Address.....

Scientific Edition

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

A. G. DuMez, Editor, Baltimore, Maryland

VOLUME XXX | *APRIL, 1941* | NUMBER 4 CONSECUTIVE No. 7

Acetanilid Studies. I. Acute Toxicity*

By James C. Munch,† Harry J. Pratt and Lilian M. Phillips

Acetanilid is a widely used drug, and its derivatives (including sulfanilamide) are increasing annually. A critical survey of the literature revealed many inconsistencies and contradictions with respect to the pharmacology, the pharmacodynamic action and the toxicity of acetanilid, and this investigation was undertaken with the hope of clarifying the situation. This paper deals only with acute toxicity; that is, with the development of death within twenty-four hours or less, after the administration of a known quantity of acetanilid. Some reports have been found on the toxicity of combinations of acetanilid with other medicaments, but this information will be considered in a subsequent paper of this series.

In searching the literature, every effort has been made to consult the original publications, because of the inaccuracies encountered in some abstracts. When possible, contact has been established with the authors of published reports to clear up any uncertainties and to prevent misinterpretation of published statements. In our laboratory studies healthy animals have been purchased from several dealers. Three lots of acetanilid have been used; all conform to the U. S. P. requirements and no significant differences were observed in the pharmacological action of any of these lots. Injections and observations were made by several of the authors throughout the entire study.

LITERATURE SURVEY

Acetanilid was introduced by Cahn and Hepp (9) in 1886. They had intended to use naphthaline as an antipyretic but acetanilid was furnished them instead. After its efficiency as an antipyretic had been established, a series of toxicity tests was started, as well as clinical investigations to determine the usefulness of this product. The material which was used at that time was probably very impure, judging by the present standards for this product. Improvements in method of manufacture have produced chemically pure acetanilid which may be even less toxic than the early product. A compilation of the studies on animals has been prepared in which the largest dose that has been survived by 50% or less of the test animals ($LD_{0\%}$–$LD_{50\%}$) is designated as the "tolerated dose" and the dose which kills all or practically all of the animals tested ($LD_{90\%}$–$LD_{100\%}$) as the "lethal dose." These values are presented in Table I. The data on frogs (7, 21, 43), mice (15, 21, 22, 25), rats (22, 48, 50), guinea pigs (21, 22, 28, 50), rabbits (10, 22, 25, 50, 57), cats (12, 42), dogs (17, 19, 20, 22, 25, 38, 42, 50, 57) and monkeys (47) have been classified in accordance with the reported

* Presented before the Scientific Section, A. PH. A., Richmond meeting, 1940.

† Consultant Pharmacologist, Upper Darby, Pa.

method of administration. The results have been reduced to mg. per Kg. of body weight. In some reports, the solvent or the suspending medium used for the preparation of the test solution has been reported, since it appeared to influence the toxicity findings.

Table I.—Acetanilid: Acute Toxicity. Literature and Laboratory Data

Animal	Method of Administration	Tolerated Dose, Mg./Kg.	Lethal Dose, Mg./Kg.	Remarks
Frogs	Heart perfusion	.....	3500 p. p. m.[a]	Stopped in 95 seconds
Mice	Oral subcutaneous	1840	.....	.....
		1200–1350	1200–1300	55% alcohol
Rats	Oral	400 (LD_{0}%)	800	LD_{50}%:acacia
	Oral	.....	1200	LD_{100}%:acacia
	Oral	.....	2400	LD_{100}%:50% alcohol
Guinea pig	Oral	.....	1400–1500	.....
Rabbits	Oral	1200	1500	.....
Cats	Oral intravenous	.....	250	.....
		.....	8.0–13.5	.....
Dogs	Oral intravenous	750–1000	700–1000	.....
		62.5–75.0	175–300	.....
Monkeys	Oral intravenous	600	.....	.....
		275	300	.....
Humans	Oral	25–500	5–250	.....

[a] P. p. m. = parts per million.

Table II.—Effect of Oral Administration of Acetanilid on Humans. Literature Data

Survived		Total Dose,	Died		
Age	Sex	Grains	Age	Sex	Remarks
5 mo.	..	3	..	..	
..	..	5	A	F	9 hrs.; no autopsy
..	..	7.5	29	M	4 hrs.; emesis, nephritis
2 wks.	..	10	..	..	
..	..	13.5	7	M	2 hrs.; no autopsy
..	..	18	22	M	10 hrs.; no autopsy
22	F	22.5	..	..	
..	..	25	33	M	1 day; epileptic, chloral, bromides for 1 year
..	..	32	C	..	1 day; no autopsy
A	M	42	..	..	
29	M	45	..	..	
A	M	60	..	..	
A	M	60	..	..	
5	M	60	..	..	
..	..	60	37	M	9 days; nephritis, jaundice
A	M	62	..		
A	M	75	..	..	
34	M	75	..	..	
70	M	75	..	..	
A	M	90	..	..	
75	M	100	..	..	
A	M	105	..	..	
A	M	120	..	..	
A	F	120	..	..	
28	M	120	..	..	
A	M	142	..	..	
A	M	170	..	..	
24	M	180	..	..	
21	M	200	..	..	
..	..	200	A	M	1 day; no autopsy
A	M	300	..	..	
40	M	450	..	..	
20	M	480	..	..	

A = Adult. C = Child. F = Female. M = Male.

Similarly, the specific information in the literature regarding the case reports on acetanilid, most of the very large number of which deal with the administration of less than 40 grains to adults, has not been included. All information dealing with death from any reported amount of acetanilid, and of survival of infants with small doses, or of adults with larger doses, has been collected (1, 2, 3, 4, 5, 6, 8, 13, 14, 16, 18, 21, 23, 26, 27, 30, 31, 32, 33, 34, 35, 36, 37, 40, 44, 45, 46, 51, 53, 54, 55, 56). The data obtained are recorded in Table II. In studying the information presented in Table II,

it may be noted that an infant, aged 2 weeks, survived 10 grains of acetanilid and an infant 5 months old survived 3 grains. In general, the large number of reports of survivals of quantities up to 40 grains were not tabulated. Specific reference is made to 4 individuals surviving doses of 60 grains; the ages of 3 were not reported, but one was a 5-year-old boy. Nine individuals (adults) survived 100 to 200 grains. One instance each was reported of survival after the ingestion of 300 grains, 450 grains and 480 grains of acetanilid by adults.

A total of 8 reports of deaths were found, as indicated in Table II. The quantities of acetanilid taken ranged from 5 grains to 200 grains. In 5 of these cases, the antemortem history was not given and no postmortem was performed, so there is no convincing scientific proof that acetanilid was the cause of death. The death of an adult female within 9 hours after taking 5 grains of acetanilid would appear to be due to idiosyncrasy, in the light of the survival of so many individuals with doses in excess of 100 grains. A man, aged 29, died 4 hours after taking 7.5 grains of acetanilid. The case history showed that he vomited most of the acetanilid immediately after taking it and post-mortem examination showed marked nephritis which might have been sufficient to cause death. An epileptic male, aged 33, who had been taking large quantities of chloral and bromides for a year, died within 1 day after ingestion of 5 grains of acetanilid. No post-mortem examination was made. A man, aged 37, died 9 days after taking 60 grains of acetanilid. Post-mortem examination showed marked nephritis and jaundice. An exhaustive search of the literature has failed to reveal any additional published records of death following the ingestion of acetanilid.

The pharmacological studies by Hale (20) in 1909 suggested that certain combinations of drugs increased the toxicity of acetanilid. Subsequent pharmacological studies indicated that other factors than acetanilid were responsible for the injurious effects noted. A report by Kebler, Morgan and Rupp (26) in 1909 presented opinions on the harmful effects of acetanilid, antipyrin and phenacetin, as indicated in replies to a questionnaire. The authors report a total of 614 cases of poisoning from acetanilid and claim 16 deaths. The original case reports referred to in this bulletin are scientifically unconvincing. Subsequent studies by Helms and Lowy (22, 29, 30) summarized the studies in the United States based on reports obtained from various hospitals over a period of 10 years. Based on a total of 25,000,000 admissions during 10 years, acetanilid was found to be responsible for 5.6 admissions per million and 0.16 death per million admissions. The admissions and the deaths due to barbiturates were ten times as large as those due to acetanilid. A survey of deaths of children 5 years and under in New York State (exclusive of New York City) in the period from 1926 to 1932, inclusive (58), showed a total of 158 deaths, of which one was due to acetanilid.

Herz (24) presented a clinical review in 1934 to show that acetanilid is a safe and useful drug. Sollman (49) states that small doses, such as 3 grains of acetanilid, may be repeated a few times at 3-hour intervals, and Cushny (11) states that acetanilid is not very poisonous. Reid Hunt and Gettler (39) stated that the fatal dose was impossible to state, since death had been reported from

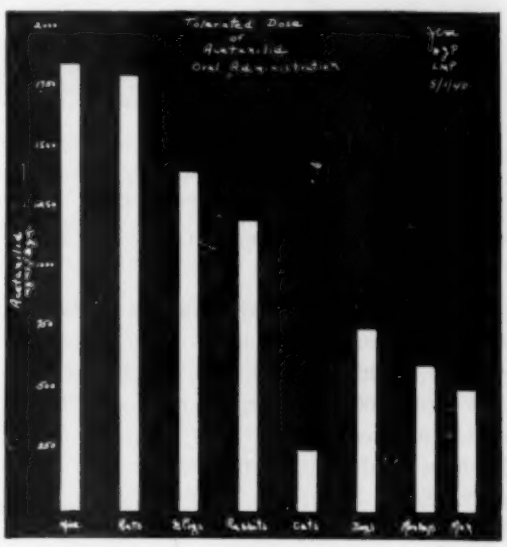


Fig. 1.—Toxicity of Acetanilid to Various Species of Animals—Oral Administration.

8 grains and recovery from doses above 120 grains. Reimann (41) reports that acetanilid produces an untoward effect in degenerative cardio-vascular renal diseases in individuals in doses of 0.6 to 1.3 grams; deaths in apparently normal humans in doses of 0.6 to

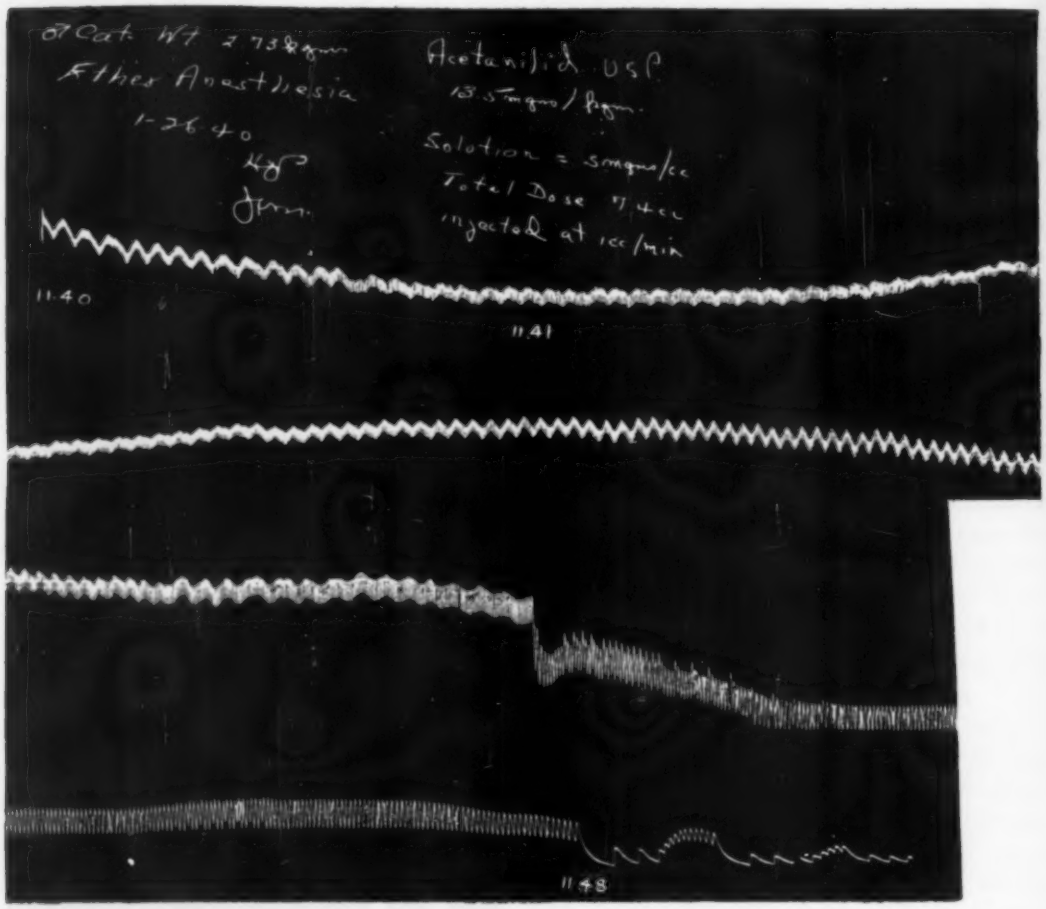


Fig. 2.—Effect on Blood Pressure of Intravenous Injection of Acetanilid to an Anesthetized Cat.

Protocol.—Male cat, 2.73 Kg., etherized, injected with solution containing 5 mg. of acetanilid per cc. in distilled water, at the rate of 1 cc. per minute. Injection was begun at 11:40 A.M., and no alterations in respiration were observed until 11:47 A.M. A slight fall in blood pressure was followed by a slight rise suddenly passing into a drop of 30 mm. at 11:47 and death at 11:48 A.M., January 26, 1940. See Fig. 2.

2 grams, although recovery followed the oral administration of 4 to 8 grams (60–120 grains). Thienes (52) states that death has followed 0.66 to 2 grams of acetanilid in children, aged or very sick patients; for a healthy adult the acute fatal dose is probably above 30 grams (450 grains). From this collection of information, the data on humans have been assembled as reported in Table I. Figure 1 was prepared to show the toxicity of acetanilid, in mg. per Kg., following oral administration to various species of animals. The ordinates are the maximum tolerated doses reported in Table I, except for rats, in which the average of the two lethal dose values was used, and for guinea pigs and cats in which the lethal doses were used, since the tolerated doses were not known. In our studies, it appeared that the tolerated doses is about 80% of the lethal dose. It is not believed that any significant error is introduced by using these values, to follow the trend of relationship between species and toxicity. Much to our surpirse, there appeared to be a definite progressive increase in toxicity of acetanilid

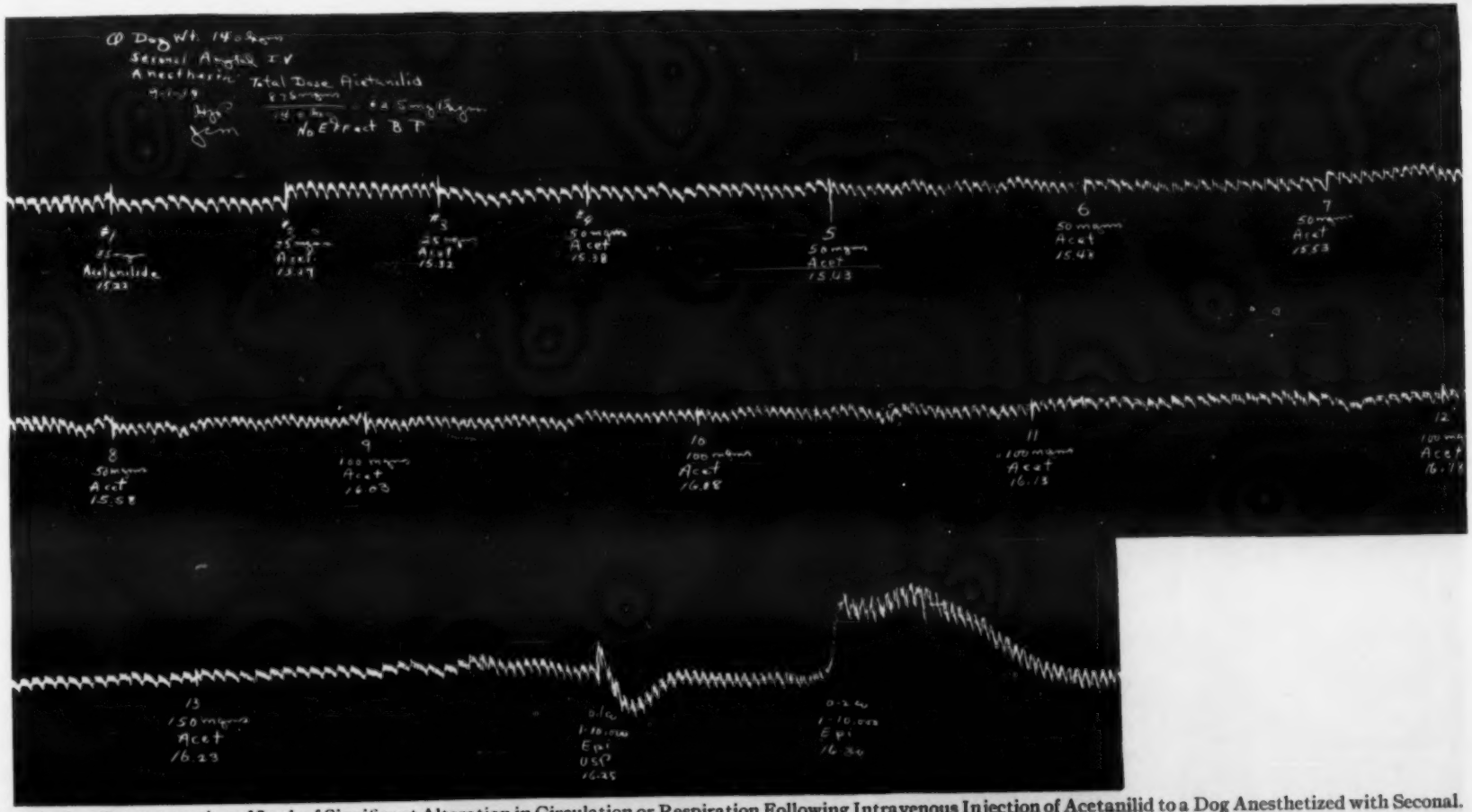


Fig. 3.—Demonstration of Lack of Significant Alteration in Circulation or Respiration Following Intravenous Injection of Acetanilid to a Dog Anesthetized with Seconal.

Protocol.—Female dog, 14 Kg., anesthetized with Seconal I.P., after a series of injections of epinephrine, was injected with a solution containing 5 mg. of acetanilid per cc. in distilled water, at 5-minute intervals. Interrupted tracings of blood pressure were made. A series of three doses of 25 mg. of acetanilid were given, the second of which caused a transient pressor response. A series of 5 injections of 5 mg. each failed to produce significant changes. A series of 4 injections of 100 mg. each caused no significant changes. A single injection of 150 mg. of acetanilid at 16:23 caused a very slight rise in blood pressure. The total dose of acetanilid administered was 875 mg., or 62.5 mg. per Kg. After this series of acetanilid injections, U. S. P. Standard Epinephrine in doses of 10 gamma and 20 gamma produced the same increases in blood pressure as the same doses had produced before injection of acetanilid, September 1, 1939. See Fig. 3.

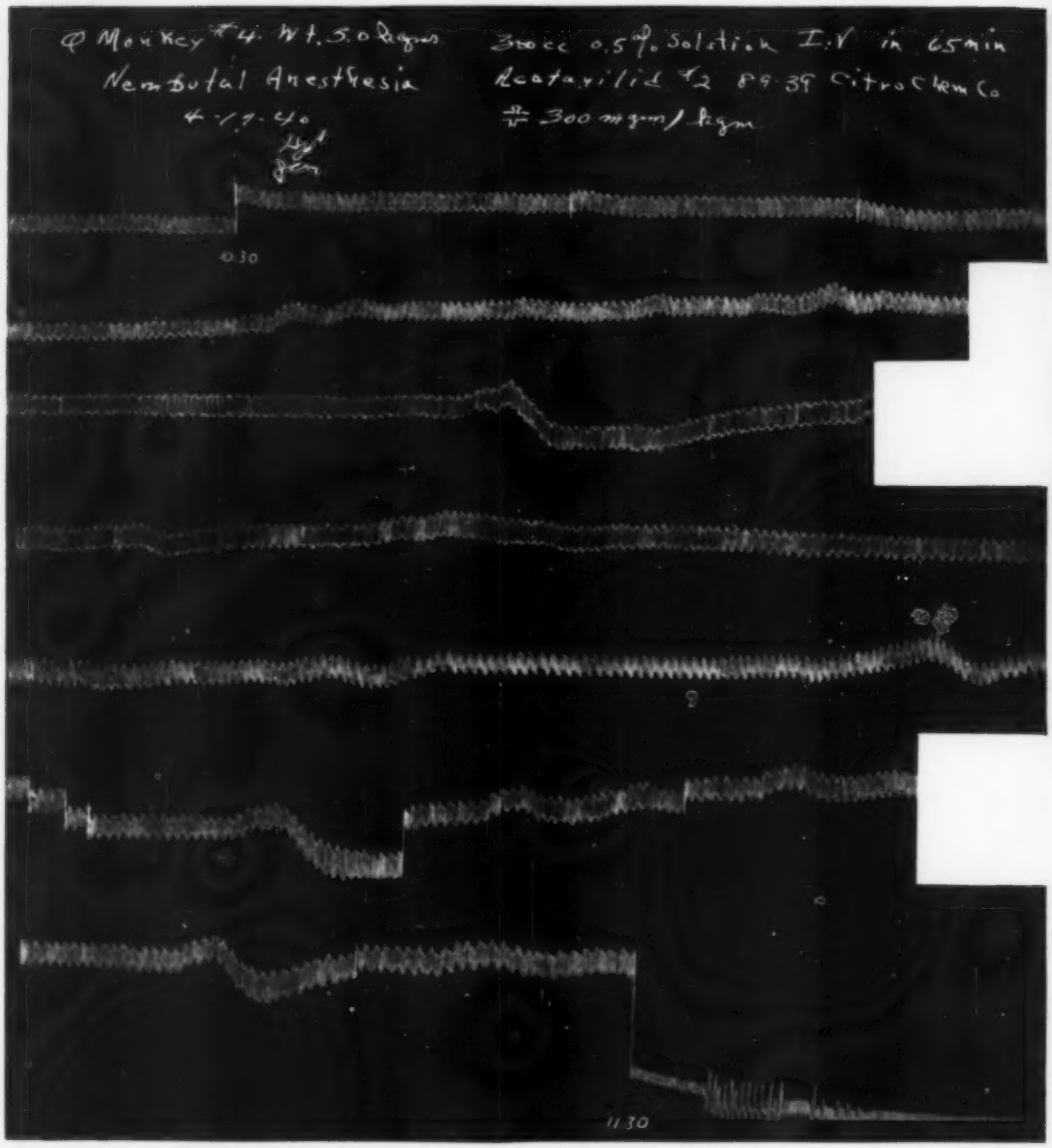


Fig. 4.—Alterations in Blood Pressure Produced by the Intravenous Injection of Acetanilid to a Monkey Anesthetized with Nembutal.

Protocol.—Female monkey, 5 Kg., anesthetized with Nembutal I.P., injected with solution containing 5 mg. of acetanilid per cc. in distilled water continuously. The first injection at 10:30 A.M. caused a prompt rise in blood pressure of about 25 mm., which gradually returned to the normal level. Slight but not significant rises and falls in blood pressure were observed during the series of injections until 11:15 when a total fall of about 20 mm. developed, followed by a rather rapid return to the normal blood pressure level. At 11:28 there was a sudden rise followed by a fall of equal magnitude, and leading to the original blood pressure again. At 11:30 there was a sudden precipitous drop of 55 mm. in blood pressure, with apnea. Death developed within 5 minutes or before 11:35 A.M., April 17, 1940. The total dose administered was 1500 mg., or 300 mg. per Kg. See Fig. 4.

when administered orally to animals, in the order of mice, rats, guinea pigs, rabbits, dogs, monkeys, man. Cats are definitely out of line in this progression, being about twice as susceptible as man. For this reason it is felt that toxicity studies conducted on dogs or monkeys are more significant for application to man than are studies on cats.

LABORATORY STUDIES

Because of the variations in tolerated and in lethadoses for animals and for man obtained in the literal ture survey, laboratory investigations were under-

taken on animals and on a group of humans. Most of our animal studies were made on cats, dogs and monkeys. Typical protocols and records of effect on the blood pressure are shown in Figs. 2, 3 and 4.

Figure 2 shows the effect on blood pressure of intravenous injection of acetanilid to a cat under ether, and the details of the experiment, which is typical of a number of cat tests, are given in the protocol. The lethal dose of acetanilid ranged from 8.5 to 13.5 mg. per Kg. of body weight, to cats anesthetized with ether.

Figure 3 and its protocol show the lack of significant alteration in circulation or respiration following intravenous injection of acetanilid to a dog anesthetized with Seconal. This animal received a total of 875 mg., corresponding to 62.5 mg. per Kg, which did not cause death.

Figure 4 and its protocol show the alterations in blood pressure produced by the intravenous injection of a total of 1500 mg. of acetanilid to a 5-Kg. female monkey, anesthetized with nembutal. The lethal dose was 300 mg. of acetanilid per Kg. of body weight, and death was produced within an hour. No significant alterations in blood pressure or respiration were observed until shortly before death.

DISCUSSION

The question has frequently been asked whether acetanilid is a "poison." The senior author has proposed that a poison might be defined as: "A substance which chemically reacts with normal living tissues with the usual effect of injuring health or destroying life." From a consideration of the information published in the literature, as well as that obtained in our laboratory studies, it does not appear that acetanilid is very poisonous, considered from the standpoint of acute toxicity. The chronic toxicity will be considered in a subsequent report.

CONCLUSIONS

1. The acute toxicity of acetanilid has been determined by literature search and laboratory studies.

2. Following oral administration, there is a progressive increase in susceptibility from mice to rats, guinea pigs, rabbits, dogs, monkeys and man. Cats are out of line, being about twice as susceptible as man. In toxicity studies, having a bearing on human interpretations, dogs and monkeys preferred.

3. No significant effects on blood pressure or respiration were observed, following intravenous injection of acetanilid solution to dogs or monkeys, until the lethal dose was approached.

4. Doses of acetanilid up to 480 grains were tolerated, corresponding to tolerated doses of 25 to 500 mg. per Kg. for humans. Eight deaths were reported in humans, following quantities ranging from 5 to 200 grains, but the lack of post-mortem examinations in 5, and the pathological conditions observed in the other 3 make it difficult to conclude that acetanilid was the cause of death.

5. Considered from the standpoint of tolerated and lethal doses for animals and man, the acute toxicity of acetanilid is relatively very low.

REFERENCES

(1) Allison, W. R., *J. Am. Med. Assoc.*, 12 (1889), 103.

(2) Armstrong, S. T., *Therap. Gaz.*, 6 (1890), 245.

(3) Austin, A. E., and Larrabee, R. C., *J. Am. Med. Assoc.*, 46 (1906), 245.

(4) Bell, G., *Memorabilien, Heilbronn*, 38 (1893), 535.

(5) Bergman, N., *Clinique* (Chicago), 27 (1906), 271.

(6) Brown, P. K., *Pacific Rec. Med. Surg.*, 13 (1898), 197; *Am. J. Med. Sci.*, 122 (1901), 770.

(7) Brown, E. D., and Morehead, D. E., *J. Pharmacol.*, 25 (1925); through reference 26.

(8) Bunce, through reference 26.

(9) Cahn and Hepp, *Berlin Klin. Wochschr.*, 24 (1887), 4, 26.

(10) Cesari and Burani, *Rass. di sci. med.*, 2 (1887); through reference 42.

(11) Cushny, A. R., "Textbook of Pharmacology and Therapeutics," 11th Edition by C. W. Edmunds and J. A. Gunn (1936).

(12) Dunker, M. F. W., and Thompson, M. R., JOUR. A. PH. A., 28 (1939), 70.

(13) Easley, E. P., *Am. Pract. and News*, 12 (1891), 178.

(14) Elmquist, "Hospitalstidende" (1904).

(15) Fantus, B., and Dyniewecz, J. M., *J. Pharmacol.*, 55 (1935), 222.

(16) Freund, through reference 26.

(17) Fröhner, E., *Monats. prakt. Tierheilk.*, 5 (1894); through reference 42.

(18) Furth, E., *Wien. Med. Presse*, 30 (1889), 652.

(19) Gibbs and Reichert, "Engelmann's Archiv, Suppl," (1892), 276; through reference 42.

(20) Hale, W., *Hyg. Lab. Bull.* (1909) 253.

(21) Hartge, A., *Petersburg Med. Woch.*, 7 (1890), 69.

(22) Helms, S. T., JOUR. A. PH. A., 22 (1933), 1093.

(23) Herrmann, E., *Deut. Med. Ztg.*, 11 (1890), 865, 875.

(24) Herz, L. H., *Internat. Jour. Med. Surg.*, 47 (1934), 104.

(25) Higgins, J. A., and McGuigan, H. A., *J. Pharmacol.*, 49 (1933), 466.

(26) Kebler, L. F., Morgan, F. P., and Rupp, P., *U. S. D. A. Dept. Bull.* (1909) 126.

(27) Kronfeld, A., *Wien. med. Wochschr.*, 42 (1892), 1457.

(28) Lepine, "La Semaine Med." (1886), 473.

(29) Lowy, O., *Can. Med. Assoc. J.*, 31 (1934), 638.

(30) Lowy, O., and Helms, S. T., *Med. Record*, 140 (1934), 561.

(31) Lundsteen, E., Meulengracht, E., and Rischel, A., *U. f. L.*, 99 (1937), 155.

(32) Lundsteen, E., Meulengracht, E., and Rischel, A., *Acta Med. Scand.*, 96 (1938), 462.

(33) Marechaux, through reference 26.

(34) *Medical Briefs*, 24 (1896), 86.

(35) Merkel, G., *Münch. med. Wochschr.*, 35 (1888), 899.

(36) Morgan, W. G., *Amer. Med.*, 1 (1906), 245.

(37) Pauschinger, *Münch. med. Wochschr.*, 36 (1889), 332.

(38) Payne, S., *J. Pharmacol.*, 53 (1935), 401.

(39) Peterson, F., Haines, W. S., and Webster, R. W., "Legal Medicine and Toxicology," Section by Reid Hunt and A. O. Gettler, 2nd Edition, Vol. II (1926), page 737.

(40) Probasco, E. B., *N. Y. State J. Med.*, 5 (1905), 318.

(41) Reimann, H. A., "Treatment in General Medicine," (1940), page 2073.

(42) Rhode, E., "Heffter's Handbuch der Exp. Pharmakol.," Vol. I (1923), page 1055.

(43) Roth, G. B., *J. Pharmacol.*, 30 (1927), 321.

(44) Sanford and Van Wagman, *J. Am. Med. Assoc.*, 48 (1907), 1693.

(45) Simpson, through reference 32.

(46) Smedley, Al. L., *J. Am. Med. Assoc.*, 48 (1907), 1433.

(47) Smith, P. K., *J. Pharmacol.*, 68 (1941), 1.

(48) Smith, P. K., and Hambourger, W. E., *Ibid.*, 54 (1935), 346.

(49) Sollman, T., "Manual of Pharmacology," 5th Edition (1936), page 586.

(50) Sollman, T., and Hanzlik, P. J., "Experimental Pharmacology," 2nd Edition (1939), page 241.

(51) Spencer, *Can. Pract.*, 16 (1891), 163.

(52) Thienes, C. H., "Clinical Toxicology" (1940), page 92.

(53) Thomas, W. H., *Indiana Med. Jour.*, 9 (1890), 67.

(54) Von Quest, E., *Kansas City Med. Index*, 8 (1887), 229.

(55) Weil, Inaug. Dissert., Paris, 1887.

(56) Wolff, J., *Deut. Med. Ztg.*, 11 (1890), 535.

(57) Young, A. G., and Wilson, J. A., *J. Pharmacol.*, 27 (1926), 133.

(58) Aikman, John, *J. Am. Med. Assoc.*, 103 (1934), 640.

Certain Salts of Atropine, Ephedrine, Epinephrine and Procaine*

By Frank M. Goyan and T. C. Daniels

It is often desirable to reduce the acidity of solutions of the hydrochlorides, hydrobromides and sulfates of physiologically active bases. In many cases this adjustment might be avoided if salts of weak acids were available to replace the salts of highly ionized acids now in use.

A recommendation that any particular salt is suitable cannot be made on the basis of the p_H of the solution alone but must, of course, await careful pharmacologic and clinical evaluation. This is shown by the work of Régnier and co-workers (1, 2, 3) who report different physiologic activity for various salts of the same base, and by Tainter, Throndson and Moose (4) who have made a careful clinical investigation of the relative merits of procaine borate as compared with procaine hydrochloride.

The report of Stover and Brigham (5) on oil-soluble procaine salts supports the conclusion that significant advances may be made by investigating different salts of the same base. This point is further emphasized by the work of Abderhalden and Vlassopoulos (6) who have shown that the presence of amino acids and polypeptides increases the physiologic activity of ephedrine and epinephrine, thus indicating the possible usefulness of salts prepared by neutralizing these bases with suitable amino acids.

A useful salt of any physiologically active base must also satisfy the requirement of stability, either in the solid state or in aqueous solution or, preferably, both. Aqueous solutions of ester-type compounds, unless stabilized, may be expected to undergo decomposition in neutral or alkaline solu-

* Contribution from the College of Pharmacy, University of California.

tions. This fact is established for procaine hydrochloride by Bullock (7) who recommends that the usual procaine hydrochloride-epinephrine mixtures be dispensed in "dry ampoules" containing the quantity of dry sterile powder necessary to yield a buffered isotonic solution when a stated amount of sterile distilled water is added. The justification for this technique is to be found in the fact that a solution having the optimum p_H for use is unstable with respect to the hydrolysis of procaine and oxidation of epinephrine. The same general difficulty is encountered in the case of atropine. Vincke and Oelkers (8) recommend that atropine be dispensed in solutions having a p_H between 4 and 5 although the best p_H for use has been reported by Gifford and Smith (9) to be approximately 7.6.

THEORETICAL DISCUSSION

A systematic study of the best procedure to be followed in preparing solutions of salts of physiologically active bases must involve considerations of the osmotic effect and p_H of the solutions as well as the stability of the preparation and the equilibrium concentration of the free base. The following equations show the type of equilibria involved in a solution of procaine salt represented by the symbol, PrHX.

$$PrHX = PrH^+ + X^- \quad (1)$$
$$PrH^+ + HOH = PrHOH + H^+ \quad (2)$$
$$PrHOH = Pr + HOH \quad (3)$$

It will be noted that the equilibria represented above may be applied generally. The formula, PrHX, would be replaced by $(NH_3)HCl$ or NH_4Cl when describing a solution of ammonium chloride. With most salts reaction (1) is complete in dilute solutions but if the salt happens to be a weak electrolyte this is not the case. Equation (2) shows that the presence of a substance capable of combining with hydrogen ion (*i. e.*, HPO_4^{--}) will markedly increase the equilibrium concentration of the free base. Bullock (7) has established this point for procaine. If the anion of the salt in question is capable of combining with hydrogen ion to form a weak acid this anion will likewise increase the p_H of the solution and the equilibrium concentration of the free base.

It is reported that solutions to be used parenterally (except intravenous) or to be applied on mucous surfaces should have a p_H equal to or slightly greater than the tissues on which they are employed. This general rule may require slight modification, however, if the equilibrium concentration of the free base becomes the deciding factor, as may be the case where too rapid absorption produces irritation. A slight modification of the p_H, not sufficient to be significant in itself, may be very important in adjusting the equilibrium concentration of the free base as indicated by equation (2). A consideration of these factors indicates that salts may be found whose simple water solution, rendered isotonic when necessary, may prove to be very useful. With this thought in mind the authors have prepared the aspartates, glutamates, levulinates and secondary phosphates of atropine, ephedrine, epinephrine and procaine. Ephedrine nicotinate was also included in the series. Preliminary attempts to produce pure salts by recrystallization from water solution failed to yield satisfactory products.

EXPERIMENTAL

Materials.—The chemicals used were obtained from commercial sources. Ephedrine hemihydrate, atropine base and epinephrine were used without further purification. Procaine was recrystallized, first from ligroin and then from a 50% alcohol-water solution. The equivalent weight of each of the bases was calculated from the results of titration with hydrochloric acid as follows: atropine base 293.2, ephedrine hemihydrate 175.2, epinephrine 188.8 and procaine 237.8. The solutions of acids were titrated against sodium hydroxide. The *l*-aspartic acid was a Pfanstiel product and the *d*-glutamic and levulinic acids were obtained from the Eastman Kodak Company. These acids were used without further purification but the primary sodium phosphate was recrystallized from water and dried to the anhydrous form. The measured concentration of the amino acid solutions was less than two per cent below the concentration calculated from the weight of the solid taken; the levulinic acid was determined to be chloride free and the primary sodium phosphate was analyzed by ignition.

Experimental Procedure.—In order to determine the exact amount of acid required for neutralization of the base for normal salt formation the authors have not relied entirely upon the weights of chemical added but have titrated the bases with different acids using a glass electrode in conjunction with the

p_H meter described by Goyan, Barnes and Hind (10). The work was done at room temperature (18–26° C.), the electrode and bridge being checked from time to time by immersion in 0.05*M* potassium acid phthalate solution the p_H of which was taken to be 4.01.

Weighed samples of the base were added to large test-tubes having a total volume of 200 cc. and oxygen-free nitrogen (pyrogallol treatment) was introduced through glass capillaries reaching to the bottom of the tubes. The nitrogen served to displace air and also for the subsequent stirring of the solutions. Dilute solutions (0.05–0.1*M*) of the different acids were prepared and titrated with a standardized solution of sodium hydroxide. Each sample of base was treated with a sufficient measured volume of one of the acid solutions to give wetting and partial solution. This was followed by the addition of water introduced in such a way as to wash the sides of the tube. Additional measured quantities of acid were then added to the tubes from time to time until complete solution was attained without complete neutralization.

A battery of four tubes was often employed and the glass electrode and agar bridge introduced into them, one at a time. The addition of acid was continued until the end-point was passed as determined potentiometrically. An additional quantity of the base was then added and, when solution was complete, enough acid was added to bring the p_H of the solution to the previously determined potentiometric end-point. This process was repeated for each acid, the resulting solutions being evaporated to dryness under partial vacuum in the tubes in which the titrations were performed. During the evaporation the tubes were held under warm water (40–55° C.) and a steady stream of tank nitrogen bubbled through the solutions. The design of the still-head used for each of the tubes was such that the evaporation could be completed in about two hours. The resulting salts were transferred to vacuum desiccators and dried over magnesium perchlorate or phosphorous pentoxide.

Results.—The results of this investigation may be divided into two sections, the first dealing with the titrations themselves and the second dealing with the properties of the resulting salts. Figure 1 shows the neutralization of ephedrine with the different acids studied, the hydrochloric acid curve being included for comparison only. For the week acids the moles of acid per mole of ephedrine were calculated from the equivalent weight of the ephedrine hemihydrate as determined by titration with hydrochloric acid, the volumes of the acid solutions and their concentrations. The hydrochloric acid curve was calculated more simply by assuming the potentiometric end-point and the stoichiometric equivalent point to be the same within the limit of experimental error.

Figures 2 and 3 refer to similar work with atro-

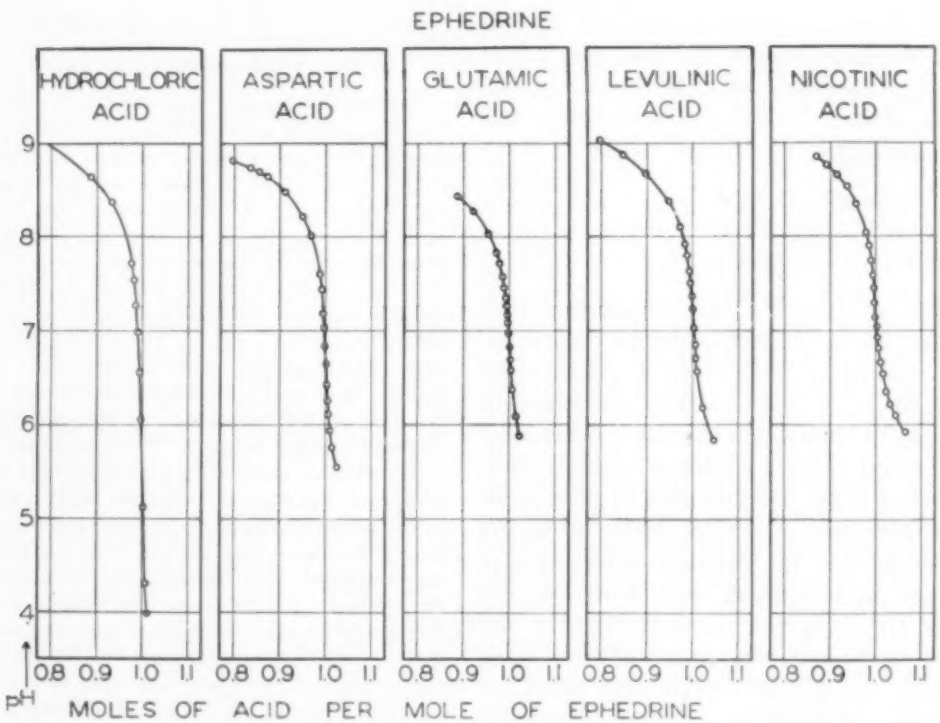


Fig. 1.—Moles of Acid per Mole of Ephedrine Calculated for the Weak Acids from the Equivalent Weight of Ephedrine Hemihydrate (175.2) Obtained from Titration with Hydrochloric Acid. The Curve for Hydrochloric Acid Was Plotted by Assuming the Stoichiometric and Potentiometric End-points to Be the Same within the Limits of Accuracy of the Work.

pine and procaine, respectively. The stoichiometric end-point for each titration of procaine and atropine with each of the weak acids was calculated from the equivalent weight determined by titrating with hydrochloric acid. This value deviated by one or two per cent from the observed potentiometric end-point. No such deviation was observed for ephedrine although the three dissociation constants do not differ by enough to account for this error. This led to the conclusion that the slight deviation was due to hydrolysis of the ester-type bases. Since the direction of the deviation confirmed this conclusion it was decided to correct the individual curves before plotting. This was accomplished by calculating the equivalent weight of each base from the titration with each of the weak acids employed and using for each base the respective average of these values.

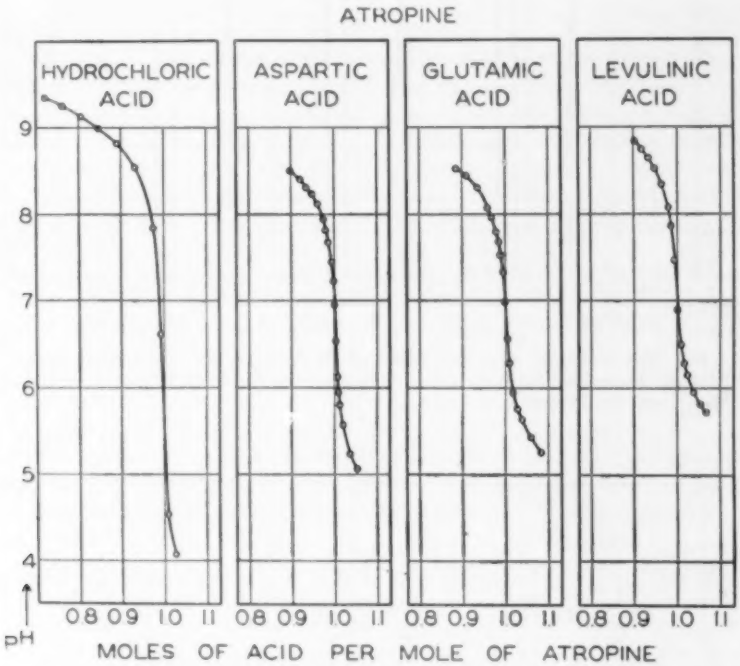


Fig. 2.—Moles of Acid per Mole of Atropine Calculated for the Weak Acids by Using the Average Equivalent Weight (295.6) Obtained by Assuming That Each Potentiometric End-point with the Weak Acids Corresponded to the Stoichiometric End-point. This Treatment Was Introduced to Correct for a Small Error Due to Hydrolysis. Otherwise the Method of Calculation Described for Ephedrine Was Followed.

This arbitrary procedure is justified because it is desirable to make the curves correspond to results obtained in the absence of hydrolysis. The equivalent weight employed in each case is recorded below the figures. Variations in the time required for the completion of the titrations and the relative alkalinity of the solutions can well account for the observed differences. Figure 4, for epinephrine, was plotted in the same manner using the equivalent weight obtained in the titration with hydrochloric acid. The technical difficulties involved in dissolving the epinephrine are apparent in the curves, although the technique used effectively prevented oxidation. Figure 5 shows the results obtained for the phosphates which were placed on a separate graph because a comparison of all of the phosphate curves seemed to be of some interest. The weakness of the acid produces curves of characteristic shape.

Calculations.—Equivalent weights of the bases recorded under the section on materials were used except as noted below the figures. *l*-Aspartic acid solutions of 0.0490*M* to 0.0492*M* were employed. The concentration of *d*-glutamic acid was 0.0497*M* and that of levulinic acid was 0.1222*M*. However, atropine and epinephrine were titrated with 0.0566*M* levulinic acid. The primary sodium phosphate was used at a concentration of 0.1005*M* and the hydrochloric acid was always 0.1000*M*. Samples of base were weighed by difference to within 0.2 mg. using calibrated weights. The final volume of the solutions titrated averaged approximately 100 cc. except in the case of epinephrine where the volume was about 150 cc. On this basis the final molal concentration of the salt solutions are recorded in the order, aspartate, glutamate, levulinate, phosphate, nicotinate as follows: ephedrine 0.013, 0.015, 0.025, 0.027, 0.022; atropine 0.0075, 0.0051, 0.0038, 0.0084; procaine 0.011, 0.013, 0.010, 0.012; epinephrine 0.0075, 0.0062, 0.0029. Only approximate values are given because the concentration of the salt does not enter into the calculations.

It will be noted that the p_H at the equivalent point (corresponding to 1.0 on each abscissa) is in good agreement with the p_H calculated by using the well-known approximate equation for obtaining the p_H of solutions of salts of weak acids neutralized by weak bases.

$$p_H = {}^1/_2 pK_a + {}^1/_2 pK_w - {}^1/_2 pK_b \qquad (4)$$

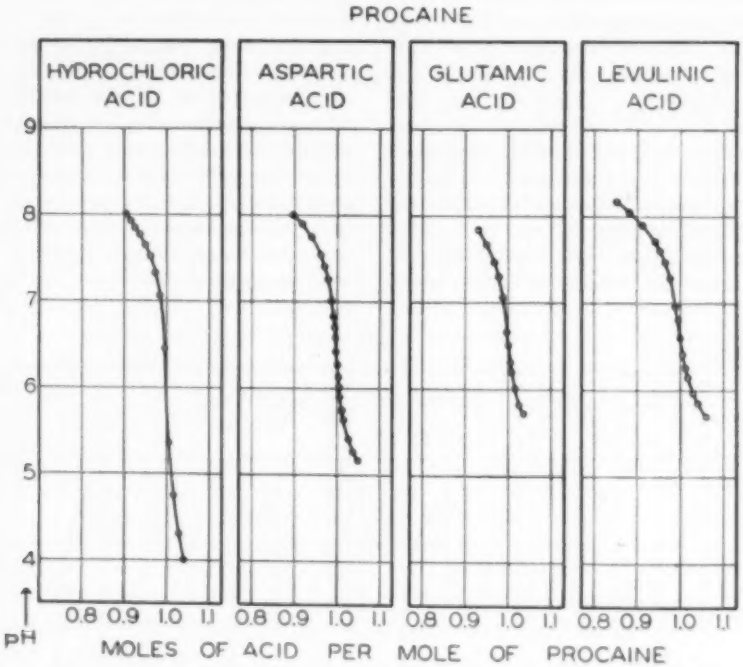


Fig. 3.—Moles of Acid per Mole of Procaine Were Calculated by the Method Described for Atropine. The Average Equivalent Weight of 241.1 Was Used for Procaine.

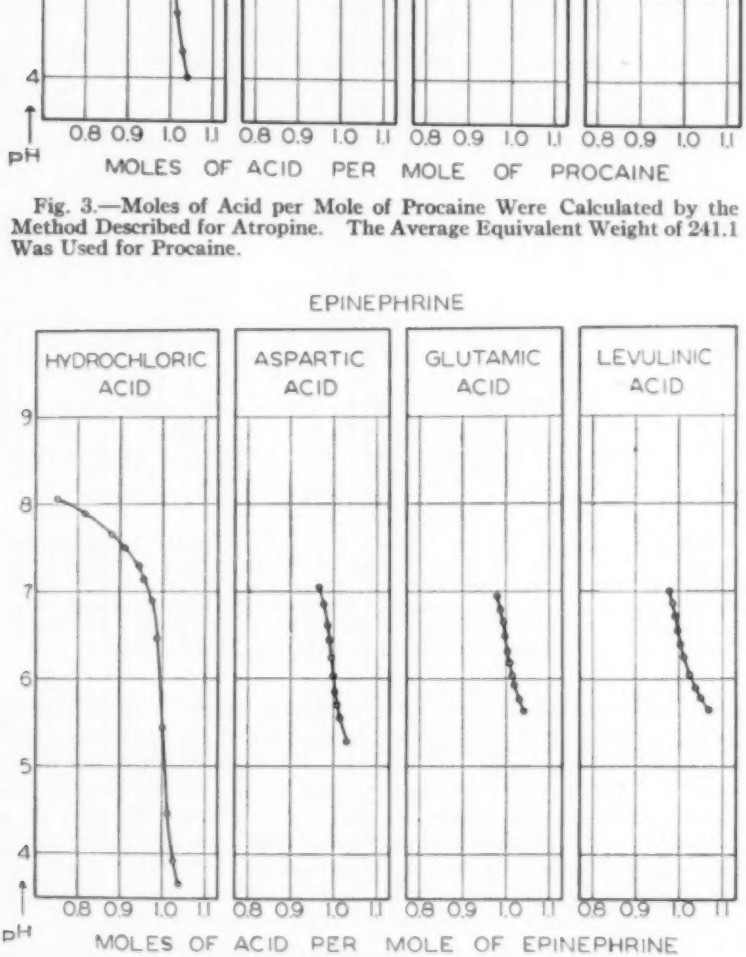


Fig. 4.—Moles of Acid per Mole of Epinephrine Were Calculated by the Method Described for Ephedrine.

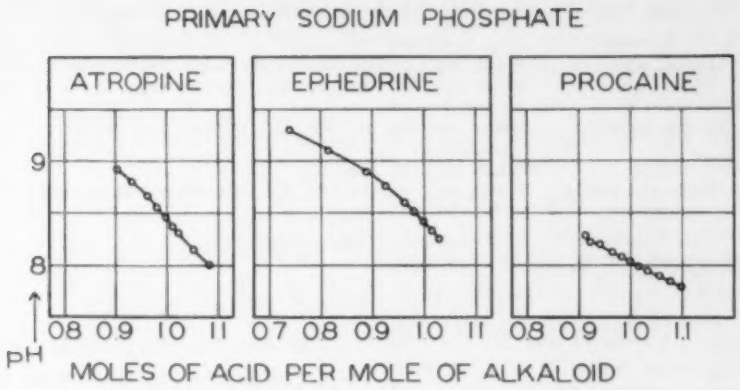


Fig. 5.—Calculations of These Curves Were Carried Out as Described for the Other Weak Acids of Figs. 1, 2 and 3.

pK_a, pK_w and pK_b refer to the negative of the logarithm of the dissociation constants of acid, water and base, respectively. Since the calculations were not intended to give results of the highest accuracy, the value of 14 was chosen for pK_w and the dissociation constants of acids and bases were chosen from the literature from the best available sources, employing values given for room temperatures. The comparison of the calculated p_H of the salts represented by the equivalent point on the curves is shown in Table I.

Solubility of Salts.—After the resulting products had been dried for several days in vacuum desiccators the approximate solubilities were determined by finding the least amount of water required to dissolve a weighed quantity of the salt. This work was done at room temperatures with constant stirring by hand. All of the salts were extremely soluble, most of them dissolving in an equal weight, or less, of water The phosphate of ephedrine deviated from this rule, 1.0 cc. of water being required to dissolve 0.164 Gm. Procaine phosphate was soluble to the extent of 0.086 Gm. in 0.12 cc. and the epinephrine salts showed slight turbidity, the glutamate in twice its weight of water, the levulinate in five times its weight and the phosphate in 100 times its weight of water. Procaine levulinate and epinephrine aspartate were viscous liquids even after standing in the desiccator for several weeks.

p_H of Salt Solutions.—At the time the solubility studies were made a portion of each salt solution was introduced into the glass electrode chamber and nitrogen was bubbled through the solution. Readings were made every few minutes and the p_H of each solution was recorded when the last two readings were the same within 0.02 of a p_H unit. The p_H values are compared with the p_H of the solutions at the end of the titrations and before evaporation. The results are given in Table II.

Discussion.—It will be noted from an examination

Table I.—A Comparison of Calculated and Observed p_H of Salt Solutions

	Atropine pK_b = 4.35 (11)		Ephedrine pK_b = 4.64 (12)		Epinephrine pK_b = 5.6 (13)		Procaine pK_b = 5.15 (11)	
	p_H Obs.	p_H Calc.	p_H Obs.	p_H Calc.	p_H Obs.	p_H Calc.	p_H Obs.	p_H Calc.
Aspartic acid, pK_a = 3.87 (14)	6.9	6.8	6.7	6.6	6.0	6.1	6.3	6.4
Glutamic acid, pK_a = 4.28 (14)	7.0	7.0	6.9	6.8	6.4	6.3	6.5	6.6
Levulinic acid, pK_a = 4.59 (15)	7.1	7.1	7.2	7.0	6.5	6.5	6.6	6.7
Nicotinic acid, pK_a = 4.80 (16)	...	...	7.1	7.1	...	...	...	...
Primary phosphate, pK_a = 7.16 (17)	8.4	8.4	8.4	8.3	...	...	8.0	8.0

Table II.—Comparison of the p_H before and after Evaporation

	Atropine		Ephedrine		Epinephrine		Procaine	
	Before	After[a]	Before	After[a]	Before	After[a]	Before	After[a]
Aspartic acid	6.75	6.53	6.52	6.16	6.14	6.15	6.38	5.98
Glutamic acid	6.95	6.82	6.86	6.34	6.32	6.30	6.43	6.37
Levulinic acid	7.03	7.03	7.00	6.58	6.52	5.94	6.67	6.70
Primary sodium phosphate	8.38	8.18	8.36	8.28	7.76	7.52	8.11	8.03

[a] These deviations may be attributed to relatively slow changes such as the hydrolysis of ester-type bases or the possible loss of volatile constituents during evaporation. The decrease in p_H of the epinephrine levulinate and epinephrine sodium phosphate may be correlated with the turbidity described under the section on solubility.

Table III.—Physical Properties of Salts Obtained by Evaporation[a]

	Atropine	Ephedrine	Epinephrine	Procaine
Aspartic acid	Deliq. white cry.	White cry., m. dec. 207° C.	Brown viscid liquid	Deliq. white cry.
Glutamic acid	Deliq. white cry.	White cry., m. 145–146° C., slow dec.	Brown cry.	Deliq. off color cry.
Levulinic acid	Deliq. paste	White needles, m. 88° C., sublimes[b]	Brown cast solid	Brown liquid
Nicotinic acid	.....	White cry., m. 118° C.	.....	.....
Primary sodium phosphate	Sinters at 100° C., white cry.	White cry., sinters 170° C., dec. 209° C.	Brown granular solid	Deliq. white cry.

[a] Abbreviations: deliq.—deliquescent; dec.—decomposes; cry.—crystals.
[b] Ephedrine levulinate may be purified by sublimation at 75° C. The purified product is a mass of loosely packed fiber-like birefringent crystals which melt at 88° C.

of the data given in Tables II and III that the technique of evaporation under a vacuum, while serving to reduce the amount of hydrolysis in procaine and atropine, does not accomplish this purpose entirely and tends to promote other changes. These factors are apparent in the data of Table II. The additional observation that the salts of procaine and atropine are deliquescent supports the conclusion that preparation of aqueous solutions of these substances is best accomplished by neutralizing the base with the appropriate acid at the time of use instead of preparing the solid salt. Vincke and Oelkers (8) have shown that buffered atropine preparations decompose in the solid state if they become slightly moist, thus indicating that hygroscopic ester-type salts may be expected to undergo hydrolysis unless kept under completely anhydrous conditions. The salts of ephedrine may be prepared and stored for use and for this reason a further study of the properties of these salts and their solutions is being undertaken together with a study of the rate of hydrolysis of the ester-type bases.

ACKNOWLEDGMENT

The authors are indebted to Dr. C. L. A. Schmidt for supplying the *l*-aspartic acid used in this work and also for his suggestion that a study of the amino acid salts of physiologically active bases should be of interest.

SUMMARY

Solutions of salts of four physiologically active bases were prepared by exact neutralization with weak acids after it was shown that recrystallization from water solution failed to yield satisfactory salts. Potentiometric titration curves are shown for the formation of aspartates, glutamates and levulinates of atropine, ephedrine, epinephrine and procaine. Similar curves are shown for the neutralization of atropine, ephedrine and procaine with primary sodium phosphate and for the neutralization of ephedrine with nicotinic acid.

The calculated p_H values for the equivalent point of each titration are in good agreement with the values read from the curves. The products prepared by evaporating the salt solutions to dryness did not in all cases redissolve in distilled water to give solutions having the original p_H. The possible significance of some of these changes are discussed.

The approximate solubilities and certain general properties of these products are given. Atropine and procaine salts of the weak acids studied are deliquescent but those of ephedrine appear to possess desirable properties. Melting points of the ephedrine salts are recorded and pure ephedrine levulinate, prepared by sublimation, is described.

REFERENCES

(1) Régnier, J., Delange, R., and David, R., *Compt. rend.*, 202 (1936), 591–592; *Chem. Abstr.*, 30, 7207.

(2) Régnier, J., Lambin, S., and Szollosi, E., *J. physiol. path. gen.*, 35 (1937), 709–734; *Chem. Abstr.*, 32, 8001.

(3) Régnier, J., and Quevauviller, A., *Compt. rend. soc. biol.*, 131 (1939), 68–69; *Chem. Abstr.*, 33, 6379; *Compt. rend. soc. biol.*, 131 (1939), 728–729; *Chem. Abstr.*, 33, 7887; *Compt. rend.*, 205 (1937), 251–254; *Chem. Abstr.*, 31, 7533. *Anesthésie et analgésie*, 2 (1936), 576–584; *Ibid.*, 2 (1937), 585–589; *Chem. Abstr.*, 31, 8685.

(4) Tainter, M. L., Throndson, A. H., and Moose, A. S., *J. Am. Dental Assoc.*, 24 (1937), 376–386.

(5) Stover, O. H., and Brigham, E. H., U. S. Patent 2,027,126, *Chem. Abstr.*, 30, 1519.

(6) Abderhalden, E., and Vlassopoulos, *Arch. ges. Physiol.* (Pflügers), 225 (1930), 558–560.

(7) Bullock, K., *Quart. J. Pharm. Pharmacol.*, 11 (1938), 407–430.

(8) Vincke, E., and Oelkers, H. A., *Med. Klinik*, 33 (1937), 80–82.

(9) Gifford, R., and Smith, R., *Arch. Ophthalmol.*, 9 (1933), 227.

(10) Goyan, F. M., Barnes, C. L., and Hind, H. W., *Ind. Eng. Chem., Anal. Ed.*, 12 (1940), 485.

(11) Kolthoff, I. M., *Biochem. Z.*, 162 (1925), 289–353.

(12) Abildgaard, J., and Baggesgaard-Rasmussen, H., *Dansk. Tids. Farm.*, 4 (1930), 30–38; *Chem. Abstr.*, 24, 2834.

(13) Goyan, F. M., Unpublished work.

(14) Schmidt, Carl L. A., "The Chemistry of the Amino Acids and Proteins" (1938), page 613, Charles C. Thomas.

(15) Ostwald, W., *Z. physik. Chem.*, 3 (1889), 193; "Beilstein," 4th Edition, III, 673.

(16) Erlenmeyer, H., Epprecht, A., and v. Meyenburg, H., *Helv. Chim. Acta*, 20 (1937), 310–312; *Chem. Abstr.*, 31, 3765.

(17) Clark, Wm. M., "The Determination of Hydrogen Ions" (1928), page 678, 3rd Edition, Williams and Wilkins Co.

A Study of Intermolecular Compounds*

By Helmut M. Haendler with L. Wait Rising†

The residual affinity possessed by various organic compounds, whatever its origin, is a property somewhat difficult, if not impossible, to measure quantitatively. To attempt the prediction of the possibility of formation of an intermolecular compound on the basis of present evidence is useless. In most cases the procedure is somewhat empirical; solutions of the compounds are mixed and an effort made to isolate any crystalline products. The application of melting point curves, however, simplifies the method considerably, and with the collection of sufficient data the prediction as to the possibility of forming intermolecular compounds can be expected to become more definitive.

Knowledge of this sort would be particularly helpful in the field of pharmaceutical chemistry, where the preparation and chemotherapy of new compounds is of great value. Consequently, it was decided to study certain pharmaceutical combinations to determine, if possible, what compounds in particular exhibit a tendency to combine in this fashion.

The "thaw-melting point" curve (1) offers the quickest and most reliable method for this type of study. It is possible to tell directly whether a compound is formed or whether the two components merely formed a eutectic mixture. As the temperature of a mechanical mixture of the two components is raised, a point is reached where the material appears to soften or "thaw." Further heating causes complete melting, and the temperatures at which these two phenomena occur are plotted against mol percentages of various mixtures of the two substances.

EXPERIMENTAL

The combinations of acetanilid, in particular, and of several other pharmaceuticals were studied. Varying amounts of the two U. S. P. chemicals of each system, dried in a vacuum desiccator, were weighed into small test-tubes, melted in an oil bath, allowed to solidify, pulverized and the melting points taken. An aluminum block, drilled for a thermometer and a capillary tube, heated by a micro burner, and equipped with a viewing microscope, was used for the measurements.

In general, one of two types of curves is obtained. In the case of a eutectic mixture, the curve is represented as in (*a*) of Fig. 1; in the event that a compound is formed, the shape assumed is that of (*b*). The point at which the thawing curve, which is the lower of the two, intersects the melting curve represents the eutectic point in the first case (*a*); the three intersections represent the two eutectics and the melting point of the compound formed, if such is the case, as in (*b*).

None of the systems observed have given evidence of compound formation. The observational data for each system studied are given in Tables I to XII. In these tables, the mol percentage of one component is given, followed by the observed thawing temperature and the final observed melting point. From graphical consideration of these data, the

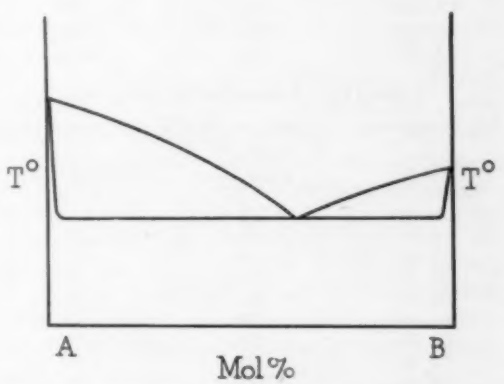


Fig. 1 (*a*).—Thaw-Melting Point Curve for a Eutectic.

* Presented before the Scientific Section, A. PH. A., Richmond meeting, 1940.

† College of Pharmacy, University of Washington, Seattle, Washington.

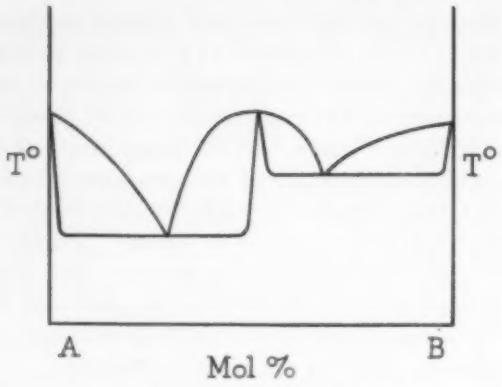


Fig. 1 (*b*).—Thaw-Melting Point Curve for a Compound.

composition and melting point of the eutectics were obtained.

Table I.—Acetanilid-Antipyrine

No compound; eutectic at 52% acetanilid with m. p. of 56° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	111	112
11.44	68	106.5
17.30	56	103
30.65	56	90
40.07	56	79
50.66	56	60.5
54.32	55	63
63.74	56	79
75.88	56	93
83.15	56	101
93.53	68	111
100.00	114	115

Table II.—Acetanilid-Mandelic Acid

No compound; eutectic at 55% acetanilid with m. p. of 58.5° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	117	119
10.04	68	112.5
19.64	58.5	107
29.46	59	99.5
40.31	58.5	86.5
50.50	58	72.5
59.20	58	71.5
71.09	58.5	91.5
79.59	59	101
90.60	58.5	109
100.00	114	115

Table III.—Acetanilid-Betanaphthol

No compound; eutectic at 52.5% acetanilid with m. p. of 59° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	121.5	122.5
9.98	60.5	115
19.94	59	107
30.57	59.5	93.5
39.93	59	80
51.18	59	61.5
60.70	59	76
73.91	59	95.5
81.24	59	101.5
91.78	60	110
100.00	114	115

Table IV.—Acetanilid-Phenacetin

No compound; eutectic at 66% acetanilid with m. p. of 83° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	136	137
10.02	83	130
20.09	83	124.5
30.11	84	118
39.91	84	112.5
49.82	83	105
58.94	83	96.5
69.81	83	91
78.76	84	98
90.23	85	107
100.00	114	115

Table V.—Acetanilid-Pyramidon

No compound; eutectic at 55% acetanilid with m. p. of 58° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	106	107
14.45	60	100
29.65	59	92
39.45	58.5	83
50.33	58.5	67.5
58.57	58	71
69.56	58	91
81.02	58	104
88.94	58	109.5
100.00	114	115

Table VI.—Acetanilid-Sulfonal

No compound; eutectic at 64% acetanilid with m. p. of 90° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	125	126
14.57	91	120.5
19.64	89.5	119
28.60	90	114.5
39.18	89.5	110
49.35	90	103.5
59.28	90	96
70.32	90.5	96
78.38	89.5	103
89.54	91.5	109.5
100.00	114	115

Table VII.—Acetanilid-Trional

No compound; eutectic at 33% acetanilid with m. p. of 61° C.

Mol % Acetanilid	Thaw Point, ° C.	Melting Point, ° C.
0.00	74.5	75.5
9.79	61.5	71.5
20.45	61	67
29.27	61	63.5
39.45	60	71
49.24	61	82
60.76	61.5	92
69.86	61	99
78.53	61	103
85.39	61	107
100.00	114	115

Table VIII.—Antipyrine-Phenacetin

No compound; eutectic at 62% antipyrine with m. p. of 76° C.

Mol % Antipyrine	Thaw Point, ° C.	Melting Point, ° C.
0.00	136	137
8.12	78	131.5
20.87	76.5	122.5
25.91	76	120
39.73	76	105
46.86	76	97
59.03	76.5	81
72.55	76	91
78.30	76	97
90.05	76	106.5
100.00	111	112

Table IX.—Mandelic Acid-Betanaphthol

No compound; eutectic at 53% mandelic acid with m. p. of 88.5° C.

Mol % Mandelic Acid	Thaw Point, ° C.	Melting Point, ° C.
0.00	121.5	122.5
9.90	91	117
19.65	90	111.5
30.35	88.5	105.5
39.94	89	99.5
50.49	89	91
59.91	88	96.5
71.26	88	105
79.64	88	109.5
90.78	90	115
100.00	117	119

Table X.—Mandelic Acid-Phenacetin

No compound; eutectic at 56.5% mandelic acid with m. p. 79° C.

Mol % Mandelic Acid	Thaw Point, ° C.	Melting Point ° C.
0.00	136	137
9.96	79	130
19.92	79	123
30.00	79	115
39.06	79	106
49.35	79	92
60.01	79	84.5
70.86	79	97.5
80.30	78.5	106
87.05	78.5	112
100.0	117	119

Table XI.—Mandelic Acid-Sulfonal

No compound; eutectic at 57% mandelic acid with m. p. of 86° C.

Mol % Mandelic Acid	Thaw Point, ° C.	Melting Point, ° C.
0.00	125	126
9.97	88.5	122
19.72	86	118.5
30.11	86	112
39.74	86	105
50.14	86	96
59.78	86	90.5
69.89	86	98.5
78.36	86.5	105.5
90.53	87.5	113.5
100.00	117	119

Table XII.—Betanaphthol-Phenacetin

No compound; eutectic at 61% betanaphthol with m. p. of 70° C.

Mol % Betanaphthol	Thaw Point, ° C.	Melting Point, ° C.
0.00	136	137
10.09	71	131
19.78	70	124
29.79	70	114
40.26	70	103
50.05	70	91
60.48	70	72
70.15	70	89
79.61	70	103
89.50	72	114
100.00	121.5	122.5

REFERENCES

(1) Rheinboldt, H., *J. prakt. Chem.*, 111 (1925), 242; Rheinboldt, H., and Kircheisen, M., *Ibid.*, 112 (1926), 187; *Ibid.*, 113 (1926), 199, 348.

Report on the Vanadium Oxytrichloride Colorimetric Method for the Determination of Capsaicin in Capsicum

By Alice Hayden and C. B. Jordan**

In July 1933 L. F. Tice (1) published in the *American Journal of Pharmacy* an article on "A Simplified and More Efficient Method for the Extraction of Capsaicin Together with the Colorimetric Method for Its Quantitative Determination in Capsicum Fruit and Oleoresin." The colorimetric assay as described in the above publication was later modified as follows (2):

ASSAY PROPER

"The sample to be assayed would be representative of the whole lot of capsicum and not having an abnormal ratio of any one of the fruit parts. It should be powdered and dried in a desiccator to remove moisture.

"Shake 1 Gm. of the dried and powdered capsicum with 50 cc. of dry acetone in a dry glass-stoppered flask, allow the mixture to stand with occasional agitation for from one-half to one hour and filter.

"Add from 0.2 to 0.3 per cent of dried, non-pungent paprika to about 100 cc. of dried acetone, in another flask, shake it well and filter. Then adjust the color to match that of the acetone extract of the capsicum already prepared, diluting it with sufficient acetone. Use this paprika extract to prepare the standard, by dissolving 7 mg. of capsaicin, accurately weighed, in 50 cc. of the colored acetone.

* Purdue University School of Pharmacy.

This standard consists of a 0.014 per cent solution of capsaicin.

"Pour 5 cc. of the clear capsicum-acetone extract (2 per cent w/v) into each of four matched test-tubes and 5 cc. of the standard solution into another matched test-tube. To the tube of standard solution add 14 drops of a fresh, 1 per cent solution of vanadium chloride ($VOCl_3$) in dry carbon tetrachloride and then 12 drops of the same reagent to the first of the unknowns, 14 drops to the second, 16 drops to the third and 18 drops to the fourth tube. Use a bulb medicine pipette in dropping the reagent.

"Allow the tubes to stand for two minutes, when at least one of the four tubes should develop a greenish blue color equal to or of greater intensity than that observed in the standard tube.

"The standard solution of capsaicin slowly decomposes and therefore must be prepared freshly as needed. All moisture must be absent in every step of the process."

The above method seemed to offer the possibility of a more scientific and accurate evaluation of capsicum than the U. S. P. X organoleptic test. The Chairman of the U. S. P. Sub-committee No. 6 therefore asked several investigators to consider the method to determine whether or not it could be used as a satisfactory test to be recommended for adoption by the U. S. P. Revision Committee. The following persons were asked to collaborate in this study:

Dr. George E. E'we, Tailby-Nason Company
Dr. Joseph Rosin, Merck & Company
Dr. W. L. Scoville, Parke, Davis & Company
Mr. R. E. Himelick, Purdue University

Dr. E'we reported his findings as follows:

"The two lots of capsicum which we have on hand each required 0.3 cc. to 140 cc. of sweetened water to allow the detection of pungency when swallowed. Since the U. S. P. X test specifies that 0.1 cc. will produce a sensation of pungency these capsicums are below the U. S. P. standard. These capsicums were from widely different sources and three individuals confirmed the degree of pungency.

"The Vanadium Chloride method of assay confirmed, in general, the organoleptic tests. The clear-capsicum-acetone extract had to be brought to a 4% strength solution (the initial colors of the extract and the standard capsaicin solution being the same) in order to obtain approximately the same intensity of bluish color in both extract and standard. Both samples of capsicum gave about the same results.

"The number of drops of Vanadium Chloride solution used influences the intensity of the color, the color increasing as the Vanadium Chloride solution is increased. The shades of bluish color yielded by the extracts and by the standard were totally different, the extracts giving greenish blue while the standard gave a 'truer' blue color.

"It would appear that the Vanadium Chloride assay method is a useful qualitative test for capsaicin and for the rough comparison of capsicum , but in view of the widely different quality of colors yielded by the extracts as against the standard and because of the variation in intensity induced by varying the amount of reagent added, its adoption by the U. S. P. would likely be productive of no more uniformity among analysts than the present test."

Concerning the assay, Dr. Rosin writes as follows:

"The colorimetric assay, while it is much shorter, has many pitfalls. In order to make the colors matchable paprika has to be used, and because of the change of the color to green with a slight excess of the vanadium oxytrichloride, several controls have to be made, etc., all of which complications do not recommend themselves very strongly. However, I may be wrong, and I hope I am. At any rate I am prepared to try out the colorimetric assay as you suggest."

Unfortunately, Dr. Rosin was not able to secure sufficient materials to perform the laboratory tests at that time.

Three samples of Mombassa capsicum, together with a sample of paprika, were supplied to Dr. Scoville for his investigations. These same samples were also used for the investigations carried on at Purdue University.

In a communication, Professor Scoville reports:

"Mr. R. T. Harris of the analytical laboratory at Parke, Davis & Company has carried out the Tice method for the determination of capsaicin in capsicums on the three samples of capsicum sent. I witnessed the tests, and since we are in agreement as to the applicability of the test, this is a joint report thereon.

"The three samples of capsicums were first tested by the present organoleptic method, and each responded to the test at a 1 to 70,000 dilution. Five men took the test in each case and all were in agreement. The paprika responded to the test at a 1 to 2000 dilution.

"The three samples to be tested varied considerably in color, numbers 1 and 2 being light in color and gave a light yellow color in acetone solution. Number 3 was darker, more reddish, and the paprika had a reddish brown cast.

"The standard acetone solution of paprika matched fairly closely that of number 3 but had a more brown shade. For the other two, the paprika was diluted one-half in order to get comparable results. But the brownish shade of paprika compared with the yellow of the other two made color comparisons difficult. On adding the vanadium oxytrichloride to them, the paprika showed a distinctly different color from that of numbers 1 and 2—the latter having a greenish tint which was lacking in the paprika. This made color comparisons difficult and much less satisfactory. Each test was made by comparing the paprika solution containing 14 drops of vanadium test, with the 12, 14, 16 and 18 drops in the capsicum solutions.

"In each case the 14-drop tubes showed the closest agreement in color after a minute or so of standing. After about 5 minutes, the 18-drop tests had faded to a green and except for depth seemed to agree more closely in shade with the 14-drop paprika test.

"The color fades rather rapidly, but this could be managed if the initial shades could be more closely adjusted so as to give more satisfactory comparisons. It seems a little unfortunate that the three samples of capsicums were all of the same strength in regard to capsaicin content, and so corresponded in the test. At least, we could detect no difference, either by the organoleptic or the Tice test.

"As a trial of the method it would have been more satisfactory if the capsicums had varied markedly in strength and so given a better indication of the different colors to be expected from different strengths. As we observed them, the differences between the colors as observed from 14 drops and 16 drops of the reagent, while clearly distinguishable, were not sufficiently marked to promise satisfactory determinations of capsaicin.

"We did not have a medicine dropper, so used a 1-cc. graduated pipette for measuring. It was difficult to regulate the finger pressure to count exactly the number of drops in so low tension a liquid as acetone, and we were not sure of our count in all cases—as when two drops or even three fell in rapid succession when only one was intended, so in the second test we dropped in the stated number of drops and also measured the liquid. The results were disconcerting—as follows:

14 drops = 0.17 cc.
16 drops = 0.16 cc.
18 drops = 0.19 cc.
12 drops = 0.15 cc.
14 drops = 0.15 cc.

Evidently we did not get the variations in the amount of vanadium solution that were intended, and this hits a vital spot in the assay.

"On the third sample we did not count the drops but measured 0.15 cc. into the paprika-capsaicin standard and 0.13, 0.15, 0.17 and 0.19 cc., respectively, into the unknowns. The results were practically uniform with the other two tests.

"As stated before, we found each of the three capsicums to correspond most closely to the 14-drop or 0.15 cc. of vanadium reagent. This would, according to Tice's calculations, make each of them a U. S. P. standard capsicum—corresponding to a 1: 70,000 capsicum.

"In its present state the test is more complicated and tedious than the official organoleptic test and we do not feel that the results

are as satisfactory. We have more doubt about the end-point and would feel less certain of variations. Probably this is due in part to the fact that we were comparing a test which is new and one with which we are thoroughly familiar and have had years of experience.

"The principal objections to adopting the Tice method for the Pharmacopœia, as we see it, is, first, the difficulty of matching the shades of the solution which is being determined with that of the standard. Capsicums, even of the same species, vary widely in color. That a color comparison is more accurate than taste-matching I do not question, provided that we have the same tints to match. But when the tints differ the determination of color intensity of one color in a mixture is difficult."

Mr. Himelick made the following observations on the assay:

"1. All three samples of the Mombassa capsicums apparently met the U. S. P. standard (0.7%). Sample No. 1 was estimated to contain 0.9% capsaicin, and samples No. 2 and No. 3 to contain 0.8% capsaicin by the vanadium method.

"2. Sample No. 3 in acetone solution had a darker, reddish color than Samples No. 1 and No. 2. It was more readily matched by acetone colored with paprika than Samples No. 1 and No. 2.

"3. The colors produced with the reagent begin to fade within a very few minutes.

"4. One drop of $VOCl_3$ solution per 0.001% of capsaicin in the standard tube does not produce the darkest blue color when an ordinary medicine dropper is used. This is highly misleading, since a substandard sample may appear to be satisfactory by this method, simply because its deepest color has been produced, whereas in the standard tube it has not.

"5. Using a more dilute $VOCl_3$ solution (say, 0.5%) and measuring it from a small burette, should improve results.

"6. I find that by preparing just one tube of unknown and one standard tube the difference in color produced is distinguishable when the tubes differ by 0.002% or more in capsaicin content (corresponding to 0.14% in crude drug), using skylight for illumination. Color experts claim northern skylight to be superior."

In view of the above findings, the colorimetric assay for capsaicin in capsicums was not recommended for adoption by the U. S. P. Revision Committee. However, it was thought that, with further study, the test might be developed and so modified that it would offer a simple and accurate method by which it would be possible to determine whether capsicums met the U. S. P. requirement (0.7 per cent capsaicin).

In order to eliminate certain difficulties and possible sources of error that had been pointed out by previous workers, and to establish the reliability of the test, a study of the colorimetric assay was undertaken with the following objectives in mind:

1. To definitely determine the time of maceration required to completely extract the capsaicin from a given sample of capsicum.
2. To determine the effect of the paprika solution on the assay.
3. To determine the effect of concentration and quantity of the reagent on the color produced.
4. To provide a permanent, non-fading color standard which would eliminate: (*a*) the difficulty and necessity of preparing capsaicin; (*b*) errors due to the instability of the capsaicin solution.
5. To determine the effects of adulterants on the assay method.

DETERMINATION OF CORRECT MACERATION TIME TO INSURE COMPLETE EXTRACTION OF CAPSAICIN IN CAPSICUM

Six domestic samples of capsicum were used in the following tests: A series of samples was weighed out (1 Gm./50 cc. of dry acetone) and maceration was allowed to take place for the following periods: eight hours, four hours, two hours, one hour and 30 minutes. On a given sample, for example, Sample No. 1 (Louisiana Sun Longs, 1935 crop), the macerations were designated (8), (4), (2), (1) and (30). All comparisons on the same sample were made at the end of the eight-hour period.

Using 5 cc. filtered portions of the acetone extracts with equal quantities of the vana-

dium reagent (quantity previously determined by the number of drops of reagent required to produce the deepest blue color), no perceptible difference could be noted in the color produced with the reagent whether the samples were macerated for 30 minutes or eight hours. Apparently the time as specified in the modified Tice assay (30–60 minutes) is sufficient for extraction of the capsaicin with acetone.

Using ether and alcohol in various extractions, however it was noted that the color depth of the extracts was increased as the length of maceration increased. This was thought to be only an indication of further pigment extraction. Using acetone, the color of the extracts varied only slightly with the longer maceration periods.

PAPRIKA

The paprika used in the preparation of the standard capsaicin solution was tested for pungency by means of the organoleptic test. Out of seven individuals taking the test, only two reported perceptible sensation on the throat with a 1.2000 dilution.

A 1-gram. sample of the paprika was macerated for one hour in 50 cc. of dried acetone. Five cc. portions of this filtered acetone extract were tested with the reagent. Only a few drops of reagent were required to produce a green coloration. In every instance the color was distinctly green—no blue color being apparent even on the addition of the first one or two drops of reagent. The green color faded very quickly —in all instances within five minutes.

Using the 0.2% to 0.3% solution of paprika in acetone for preparing the standard capsaicin, it was a fairly simple matter to match the yellowish amber colored capsicum extracts. It was noted, however, that upon the addition of the reagent, it was sometimes very difficult to make satisfactory color matchings between the standard tube and the unknowns. This difficulty had been noted by previous workers and was expressed by Dr. E'we as follows: "The shades of bluish color yielded by the extracts and by the standard were totally different, the extract giving greenish blue while the standard gave a truer blue color."

As has been pointed out before, the green color obtained by the reagent with the paprika solution fades very rapidly, and the color obtained with capsaicin alone is blue. In order to obtain the best results, the reagent should be added to the unknowns first (since the color seems to persist longer with the capsicums) and the comparisons should be made as soon as the reagent has been added to the standard tube of paprika-capsaicin solution.

EFFECT OF CONCENTRATION AND QUANTITY OF REAGENT UPON COLOR PRODUCED

Vanadium oxytrichloride is a sensitive reagent and in a 1 per cent solution it is frequently difficult to determine the exact end-point of the color reaction (greatest depth of blue color without an excessive greenish cast). Since a single drop of the reagent is capable of producing quite a marked color change, it is suggested that the reagent should be made up quantitatively to insure uniform concentration. A more dilute solution of the reagent (0.5%) enables one to distinguish the end-point more readily.

The use of a small burette or a graduated pipette for adding the reagent in place of the medicine dropper and measuring the quantity of the reagent gave results which were much more readily duplicated than the dropper method. However, in using this type of apparatus one must take precaution to avoid unnecessary exposure of the reagent to air or moisture since it shows the unstable character of the pentavalent vanadium halides in that it undergoes rapid hydrolysis and thereby becomes coated with red flakes of vanadium pentoxide.

In order that different workers may secure more concordant results, it seems pertinent that the reagent should be quantitatively prepared in more dilute solution (0.5%). The inaccuracies introduced by the use of non-uniform medicine droppers and by counting the number of drops added may be eliminated by the use of a small burette or a graduated pipette for adding the reagent.

Attempts were also made to determine if more permanent and more readily comparable results could be obtained using the paper or spot test methods, but these offered no improvement over the tube method.

ATTEMPT TO PROVIDE A NON-FADING COLOR STANDARD

Authorities usually consider that a satisfactory color test should provide colors which are stable and matchable for a period of at least twenty minutes. As has been previously stated, the reagent ($VOCl_3$) produces a blue color with capsaicin. A greenish blue color may be obtained with the use of a paprika-capsaicin solution but the green color fades very rapidly, thus making the comparison with the unknowns extremely difficult unless the comparisons are made immediately following the addition of the reagent to the standard tube. An attempt was therefore made to produce a permanent, non-fading color standard in order to:

(1) increase the period of time in which reliable color matchings of the standard with the unknowns could be made;
(2) eliminate the difficulty and necessity of preparing capsaicin;
(3) eliminate possible source of error due to instability of the capsaicin solution.

The following colorimetric solutions (see U. S. P. XI, p. 557) were prepared: Cobaltous Chloride, Ferric Chloride and Cupric Sulfate. Some of the colors produced under Green (*M*, *N*, *O*) were satisfactory as matches of the standard capsaicin tube. The colorimetric solution of copper sulfate did not afford a blue color of sufficient intensity to be used, so a solution of twice the strength was prepared. This, together with a very small quantity of the ferric chloride solution, produced a fairly satisfactory match of the capsaicin-paprika standard tube. The addition of cobaltous chloride was not necessary and did not seem to affect the color sufficiently to warrant its addition.

EFFECT OF ADULTERANTS ON THE ASSAY

Using paprika, it was pointed out that a 1-Gm. sample of the material used for making the colored acetone (non-pungent paprika), when macerated with 50 cc. of dried acetone, gave a quickly fading green color when a few drops of the reagent ($VOCl_3$) were added to the clear filtrate. In Tice's (1) original article he says, "The use of a dried acetone w/v extract of paprika as the solvent in preparing the standard was found to result in a closer matching of the unknowns with the standards, the reason being that the $VOCl_3$ reacts with the coloring principles of both capsicum and paprika similarly."

A check of the literature disclosed that previous workers had noted other color reactions with the reagent, gingerol and vanillin being mentioned specifically. A number of crude drugs were selected, some because they were known to possess pungency and others simply because they were closely related to drugs which gave color reactions with the reagent, and 1-Gm. samples were macerated for 30 to 60 minutes with 50 cc. of dried acetone. Color reactions were noted with the following when the reagent was added to the clear filtrates:

Ginger
Cloves
Tumeric
Uva Ursi
Sassafras

No color change was noted with the clear filtrates of the following upon the addition of the reagent:

Curry Powder
Black Mustard
Anise
Fennel
Cubeb Berries
Cardamon Seed
Zeodary

The colors produced varied considerably with the drug and the quantity of the reagent added. Using some drugs, however, it was possible to approach very closely the color produced with an acetone extract of capsicum or with the paprika-capsaicin-acetone solution and the reagent. For example, ground drugs which gave no test at all with the reagent (see list above) could be treated with a very small quantity of ground ginger so that the acetone macerations produced a filtrate, which, with the reagent,

gave color tests which approximated the standard capsaicin color very closely. Using paprika or a sub-standard capsicum, it was a very simple matter to "doctor" the sample so that it gave a color which would indicate a standard capsaicin content.

Noting that the crude drugs giving a color reaction with the reagent all contained phenols or phenolic compounds as the principal constituents, other phenols were dissolved in acetone and tested with the reagent. Color reactions were produced with the following:

Phenol
Guaiacol
Hydroquinone
Resorcinol
Vanillin
Thymol
Salicylic Acid
Oil of Bay
Oil of Pimenta
Oil of Cardamon
Oil of Thyme
Oil of Cloves
Oil of Nutmeg
Oil of Chenopodium

Here again, the colors varied considerably, depending upon the concentration of the phenol and the amount of reagent added. Some of the colors produced faded in a short time—the green colors seeming to fade more rapidly than the blue. The color of the standard tube could be so closely matched by some of these phenols that it was impossible to distinguish the tube containing capsaicin from the one which was capsaicin-free.

Of course, it is realized that not all of these substances could be satisfactorily used as adulterants. Most of the oils, for example, could be quite readily detected by their odors. In other instances, a careful microscopic examination in conjunction with the organoleptic test would probably detect an adulterated sample. However, the mere fact that an acetone extract of a given sample, when treated with the reagent, produced a color which would match a standard capsaicin-paprika-acetone solution with the reagent, would not suffice as a satisfactory qualitative test for capsaicin in capsicum and hence could not be developed into a satisfactory quantitative method of evaluating capsaicin content.

The reaction of vanadium oxytrichloride with phenols in acetone solution seems to be quite a sensitive test and might be developed as a satisfactory generic method of distinguishing this group of compounds.

CONCLUSIONS

1. The maceration period of 30 to 60 minutes is sufficient to extract the capsaicin from capsicum using acetone as the solvent.
2. The duration of the reliable color in the standard is not long enough to insure satisfactory matchings with the unknowns.
3. A permanent, non-fading color for the standard may be achieved by using colorimetric solutions of cupric sulfate and ferric chloride.
4. More concordant results are obtained by using a weaker solution of the vanadium oxytrichloride (0.5 per cent prepared volumetrically), and measuring the reagent from a graduated pipette or a burette instead of using the dropper method.
5. A number of substances containing phenolic compounds gave color reactions with the reagent. In some instances, the colors produced approximated the standard so closely that a color test using vanadium oxytrichloride would not serve as a reliable qualitative or quantitative test for capsaicin.
6. Further investigation might prove vanadium oxytrichloride to be a sensitive generic test for phenolic compounds.

REFERENCES

(1) Tice, L. F., *American Journal of Pharmacy*, 105 (1933), 320.

(2) Tice, L. F., Mimeograph form received with communication.

"Never utter these words: 'I do not know this, therefore, it is false'. One must study to know; know to understand; understand to judge"—APOTHEGM OF NARADA

Pharmaceutical Emulsions. II. A Study of the English Method*†

By William J. Husa‡ and Charles H. Becker**

INTRODUCTION

In an earlier paper (1) a study was made of the Continental method of emulsification. The present investigation is devoted to a study of the English method of emulsification.

EXPERIMENTAL

Materials and General Methods.—The materials and methods of procedure were the same as described in a previous paper (1). In the tables, "Oil Sep." is used to indicate oil separation. The following abbreviations are used to indicate the average size of the oil globules: *A*, average diameter less than 2.5 microns; *B*, average diameter from 2.5 to 4 microns; *C*, average diameter from 4 to 6 microns; *D*, average diameter more than 6 microns.

Rate of Addition of Oil to Mucilage.—Sixty cc. portions of 12½% oil emulsions were prepared using in each case the 4:2:1 proportion and employing a No. 1 wedgwood mortar and a No. 1 wedgwood pestle. Throughout, the 2 parts of water and 1 part of powdered acacia were triturated well until a clear and uniform mucilage resulted. The 4 parts of oil were added to the mucilage in various ways.

The results show that it is best to add the oil gradually to the mucilage rather than all in one portion. Only castor oil produced an emulsion when the oil was added all at once to the mucilage. Addition of the oil gradually in one cc. portions to the mucilage produced just as good emulsions as when the oil was added dropwise.

Variation in Proportion of Acacia.—When varying the proportion of acacia, the proportion of oil and water was kept constant throughout. A No. 1 wedgwood mortar and a No. 1 wedgwood pestle were employed. If, for example, 60 cc. of the 12½% oil emulsion were prepared using 0.2 part (0.37 Gm.) of acacia, then 4 parts (7.5 cc.) of oil and 2 parts (3.75 cc.) of water were used to make the primary emulsion. The powdered acacia and 2 parts of water were first triturated together until a clear and uniform mucilage resulted, and then the 4 parts of oil were added in one cc. portions, triturating the mixture well until the oil was emulsified before the next portion was added. After addition of the total quantity of oil, the mixture was triturated for 5 minutes and then the remainder of the water was added slowly with trituration. Results of the effect of variation in proportion of acacia are given in Table I.

Table I.—Variation in Proportion of Acacia

Parts of Acacia*	Linseed Oil		Cod Liver Oil		Castor Oil		Mineral Oil	
	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion 3 Hours	Average Size of Oil Globules
1.0	Creaming	*C*	Stable	*A*	Stable	*A*	Creaming	*B*
0.8	Oil sep.	*D*	Stable	*B*	Stable	*B*	Creaming	*D*
0.6	Oil sep.	*D*	Creaming	*C*	Creaming	*C*	Creaming	*D*
0.4	Oil sep.	*D*	Creaming	*D*	Oil sep.	*D*	Oil sep.	*D*
0.2	Oil sep.	*D*	Oil sep.	*D*	Oil sep.	*D*	Oil sep.	*D*

* Number of parts of acacia used for 4 parts of oil and 2 parts of water.

Table II.—Variation in Proportion of Acacia (Continental Method)

Parts of Acacia*	Linseed Oil		Cod Liver Oil		Castor Oil		Mineral Oil	
	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules	Appearance of Emulsion, 3 Hours	Average Size of Oil Globules
1.0	Creaming	*C*	Stable	*A*	Stable	*A*	Stable	*B*
0.8	Creaming	*C*	Stable	*A*	Stable	*A*	Creaming	*C*
0.6	Oil sep.	*D*	Creaming	*B*	Creaming	*C*	Creaming	*D*
0.4	Oil sep.	*D*	Creaming	*C*	Oil sep.	*D*	Creaming	*D*
0.2	Oil sep.	*D*	Oil sep.	*D*	Oil sep.	*D*	Oil sep.	*D*

* Number of parts of acacia used for 4 parts of oil and 2 parts of water.

Results of Table I show that a decrease in the amount of acacia caused an increase in the average size of the oil globules. When using less than 0.8 part of acacia, all emulsions showed creaming or oil separation within a period of three hours of standing. When using the Continental method similar results were obtained (1).

For the purpose of comparison, an experiment was carried out with the Continental method of emulsification using one and less than one part of acacia to see which method of making emulsions was preferable when using less than 1 part of acacia for 4 parts of oil.

---

* Presented before the Scientific Section, A. PH. A., Richmond meeting, 1940.

† This paper is based on part of a thesis presented to the Graduate Council of the University of Florida in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

‡ Head Professor of Pharmacy, University of Florida.

** Graduate Scholar, University of Florida, 1939–1940.

Employing a porcelain pestle, 15.0 cm. in length and 4.5 cm. in diameter at the base, and a No. 1 wedgwood mortar, 60 cc. portions of 12½% oil emulsions were prepared. The acacia and 4 parts of oil were first triturated well, and then the 2 parts of water were added all at once; the resulting mixture was triturated for 5 minutes, and the remainder of the water was added gradually to volume. The results are given in Table II.

The results show that the English method has very little advantage over the Continental method when using less than 1 part acacia. The two methods give practically the same results.

Fifty Per Cent Emulsions.—Experiments were carried out with 50% oil emulsions to see whether or not the results obtained with the 12½% oil emulsions would be applicable to emulsions containing a higher percentage of oil.

It was found that the 50% oil emulsions showed less creaming than the 12½% oil emulsions when standing over a period of three hours. In other respects, the results of experiments with 50% oil emulsion were in agreement with the results obtained with 12½% oil emulsions.

DISCUSSION OF RESULTS

Results of the English method of emulsification show that this method has no advantage over the Continental method with respect to appearance and stability of the finished product as well as the range of emulsification and the average size of the oil globules; both methods of emulsification appear to give the same finished product. However, it takes about twice as much time to make 60 cc. of an emulsion by the English method as it does by the Continental method. Fifty per cent oil emulsions were found to show less creaming than 12½% oil emulsions.

A search of the pharmaceutical literature reveals that little or no work has been done on the English method of emulsification from the scientific standpoint. Textbooks on pharmacy are not in accord concerning the various factors and techniques of this method.

The present study brought out several interesting conclusions. With reference to the rate of addition of the oil to the mucilage of acacia, results showed that it is better to add the oil gradually rather than all in one portion. Time of trituration of the emulsified oil mixture, that is, that mixture which resulted when the 4 parts of oil was added to the mucilage of acacia, seemed to be the most important factor in the production of a more stable emulsion. Addition of the oil gradually in one cc. portion to the mucilage produced just as good emulsions as when the oil was added dropwise.

With respect to variation in proportion of acacia, when using one part and less than one part of acacia for 4 parts of oil, data showed that a decrease in the amount of acacia caused an increase in the average size of the oil globules. The use of less than 0.8 part of acacia resulted in creaming or oil separation in all emulsions within a period of 3 hours of standing; when using the Continental method similar results were obtained.

The commonly accepted belief that a small amount of acacia will emulsify a large quantity of oil, when using the English method, does not appear true, since this method showed scarcely any advantage over the Continental method with respect to range of emulsification.

SUMMARY

A detailed study was made of the English method of emulsification. Results showed that this method has no advantage over the Continental method with respect to appearance and stability of the finished product as well as the range of emulsification and the average size of the oil globules; both methods of emulsification appear to give the same finished product. However, it takes about twice as much time to make an emulsion by the English method as it does by the Continental method.

The commonly accepted belief that a smaller proportion of acacia may be used in the English method than in the Continental method is shown to be incorrect for all practical purposes.

REFERENCE

(1) Husa, William J., and Becker, Charles H., JOUR. A. PH. A., 30 (1941), 83.

(*To be continued*)

Le Clergé et la Pharmacie

Essai sur le rôle du Clergé et plus particulirement des Congrégations religieuses dans la préparation et la distribution des remèdes avant la Révolution; a review of the book by J. Tournier, I

*By K. L. Kaufman**

A brief notice of this book (1) appeared in the *Journal de pharmacie et de chimie* (2) over a year ago. After some difficulty, a copy was obtained. The material covered a phase of Historical Pharmacy which was sadly neglected in the writings of our own country. Once procured, the book seemed to be of enough interest to review for this group.

* Assistant Professor Medical College of Virginia, Richmond, Va.

The subject matter is well referenced, though little of the original material would be available in our United States. Where comments appear in this review, they are to be attributed to the original author and not the reviewer.

PREFACE

In addition to the usual acknowledgments for assistance rendered, it is made clear that much material has been obtained from the Bibliotheque Mallet and the Hôtel-Dieu, of Pontoise, and the Bibliotheque Nationale.

It seems that religious workers were never content with their status as distributors of ordinary remedies to the poor. Rather, they preferred "to profit in the prestige they exert on the public to become makers and vendors of remedies. . . .One understands, then, that the clergy had been for the apothecaries' corps a dangerous and disloyal competitor . . . ."

INTRODUCTION

Tournier has described briefly the role of the pagan priesthood in relation to pharmacy and medicine. Their collection of plants at the great sun fete of the summer solstice was continued into Christian times, though with slightly changed significance. Among the plants mentioned as used in ancient times were the orpins for burns and fever, houseleek for corns, St. John's wort for its essential oil, lavender, etc. In addition to plants of real efficiency, many were used for purely magical powers. Examples of this sort are the oak, mistletoe, boxwood, vervaine, betony, sage, wormwood, burdock, sorb, etc.

The presence of the pagan priest at the herb collection was regarded as essential to the acquisition of medical properties. A definite ritual and ceremony accompanied the gathering of the plants. A "Prayer to the Earth," taken from one of these ceremonies, follows. (The translation is somewhat free.)

The monk who has compiled this document has given it the title: "Priere à la Terre, que prononçaient les anciens paiens, quand ils voulaient récolter des herbes."

"Oh Earth, sacred divinity, mother of nature, which produces and reproduces all, tutelary planet to the humans, of which the domain is encircled by the sea and the sky, where nature is calmed, and where light comes again when night is fled, oh you who recover again the dead with your riches and the immensity of your bosom, you who contain the winds, the rains, and the tempests and unleash them at your will, you who raise the seas, who banish the sun and cause the storms; oh you who when you wish well dispense us serene days and with a constant fidelity furnish us all that is necessary to our existence; oh you in whom we take refuge when we quit this life, since all you create returns to you, you have well merited the name of Mother of the nations and of the gods, without whom nothing can be born, or die. You are great, you are the Queen of the Gods, oh diety, I adore you and your name comes naturally to my lips. Grant it that I ask of you, oh diety, and I shall render to you the actions of grace inasmuch as you deserve my gratitude. Excuse me and assist my designs. It that I ask of you, oh diety, grant me. Beget you all the herbs and distribute them to all the nations to give them health. Put in them all the beneficial virtues of which you are the dispenser, to the end that all I shall do with them be wholesome and that whoever shall receive them of my hand shall be healed. I pray to you, oh diety, grant it that I ask and beg."

The idea of the priest as healer and intermediary between the sick and the sickness is not confined to pagan antiquity. "The Christian tradition at its best, the Gospels, sees in Jesus Christ the Savior of souls and the 'Healer' of the body." The author then lists some of the works of art, and Murner's "Voyage aux Bains Mystiques" in which Christ is represented as practicing pharmacy and medicine not humanly, but "divinely."

To Cassiodorus (b. 468), Tournier attributes the beginning of the pharmaceutical movement among religious workers. This reached full bloom in the late Middle Ages. Cassiodorus recommended to the monks that they learn to ". . .distinguish each kind of plant," that they "mix with care the diverse species of drugs," and that they study the works of Dioscorides, Hippocrates, Galen and Coelius Aurelianus.

The monastic orders received the ideas of Cassiodorus quite favorably in many cases. As evidence, one notes the Benedictine Medical School at Salerno, and similar projects by the Franciscans. In tenth century France, many convents had an "Apotecarius" who filled the roles of doctor and pharmacist. One of these became quite famous for a medicinal wine compounded for use in "Cardiac crises."

In 1309, the Dominican convent at Montpellier sheltered more than sixty monks who taught pharmacy to priests of all nations. Some apothecary monks ". . .enjoyed lordly prerogatives" among the communicants, so important were they considered.

The secular clergy also prepared and distributed remedies, many of which seem rather odd. Among the examples given are: dust from the tomb of a saint, wax of candles which burn in the tomb and plants preserved near the tomb.

The remedies compounded by the monks seem to be taken from a very few source books. Nicolas de Gorram, a thirteenth century monk, has left a manuscript with a number of formulas for frictions, ointments and plasters. A few others of the fourteenth and fifteenth centuries are cited.

Monastery gardens were the source of a great many of the plants used in the medicines. For example, those at St-Germain-des-Prés furnished licorice, olive, myrtle, pomegranate, orange, rose, thyme, lily, etc. The monks charged with the collection of the herbs kept a catalog of the plants. The Benedictine Walafrid Strabus thus compiled his "Hortulus" of simples which grew in his monastery gardens. Included were sage, rue, mint, agrimony, poppy, etc.

"One may say that by their taste for classification, for order, and for methodic work, the monks had all the necessary qualities to be good apothecaries. We shall see that they were also excellent merchants."

CHAPTER I

Numerous edicts and orders on the subject of secret remedies were made by the civil authorities. More rarely, there were direct attacks of public powers on the clergy, usually cases in which the former offered their opinions to settle discussions between the apothecaries and the clergy. Among the examples of such, one may cite: the action of the Toulouse Parliament (1691) prohibiting the sale and distribution by all clergy of any drugs or medicines except to their own religious communities; the 1695 decree of the Faculty of Medicine against all religious workers who made medicines and went into homes to treat people; the 1708 ordinance of Nancy which limited the religious workers to the preparation of remedies for their own needs; the prohibition by the Council of State (1698) from the ". . .exercise of pharmaceutical roles on pain of 50 livres fine, confiscation of their remedies, and imprisonment for one year at 20 leagues from the place at which they gave the remedies. . . ." The Faculty of Medicine had the power to make the arrests. This latter prohibition was reënforced by Royal Edict in 1707, which increased the fine to 500 livres. Other similar regulations took effect in Cambrai (1799), Nancy (1665) and Bordeaux (1678).

In 1756, one finds the civil authority at Rodez prohibiting surgeons, religious workers and others from the practice of pharmacy there ". . .if they have not been accepted as masters of this art."

Finally, the royal declaration of April 1777 confirmed the Edict of 1707 (*q. v.*). A few exceptions had been made to these prohibitions. The most outstanding of these special dispensations were those to Brother Célestin to make his "Specific Remedies," and to the Carmelites to distribute their "Eau Mélisse." The first took the form of an ordinance preventing apothecaries, surgeons and physicians from interfering with Brother Célestin under penalty of 1000 livres fine, plus costs. The second was issued by the King in 1780 as a patent. The application for the letters patent specified that they would pay annually a sum of 1000 livres to the apothecaries for this privilege.

The apothecaries did not lack in defending themselves against their competitors. Vigorous protests were frequently made. In this connection, the following quotation from Lemery's "Chimie" (1756 Edition) is of interest: ". . .It is necessary to know that this pretended Eau de Mélisse is the famous water of the Carmelites of which the obstinate public without foundation wishes to attribute the secret to these ecclesiastics, although it is only on their part a usurpation from the Profession of the Apothecaries who are all able to prepare it as well and as good as these. . . ."

The decisions were rather generally approved by both public and physicians, for they prevented to some extent the exploitation of so many secret remedies. Letters are reproduced which show the violent feelings against secret nostrums and their religious inventors.

While occasional writers after Cassiodorus had urged the practice of pharmacy on the clergy, the official viewpoint of the Church often disagreed. The Councils of Clermont (1130), Reims (1131), Latran (1135), Montpellier (1162), Tours (1163), Montpellier (1195) and Paris (1212) all forbid the clergy to practice pharmacy and medicine. Some popes made exceptions, however, while some orders (*e. g.*, St. Francis) forbid themselves to practice pharmacy.

CHAPTER II

Role of the Female Religious Workers in Hospital Pharmacies

The Hôtel-Dieu at Paris installed an apothecary in 1495 and placed in charge two religious workers and a domestic.

Strangely enough, the sisters were sometimes forbidden any medicine when they were ill, as it was collected for the poor. Eventually, some hospitals gave most of the work to an "apothecary," often a mere boy, the nuns retaining supervisory powers. However, it appears to be a common complaint among the physicians that the sisters did not follow directions either as to quality or quantity of drugs in the precriptions, and often advised the patients against the use of certain medicines.

Finally, the posts of Inspector and of Apothecary-in-Chief were created with a view to remedying the situation. That this was not completely successful is shown by the continued troubles at such places as Alençon, where the apothecaries charged that several deaths were caused by the improper activities of the sisters. The pharmacists even complained directly to Mme. de Pompadour, but the city officials and others usually took the part of the nuns. A similar battle was waged at Auxonne until 1712, when the Archbishop of Besançon finally gave the sisters at that (Auxonne) hospital the right to sell to anyone in the city provided the profits be used for the benefit of the poor.

The "Suc de Réglisse," made by the nuns at Blois, became a very famous preparation. It was widely imitated.

The St. Laurent Hospital at Chalon-sur-Saone contains an interesting copper plaque in memory of a Sister Ponoard (d. 1682), who left 6200 livres, the income from which was to be used to buy drugs and sugar for making free medicines for the poor. The lady in question was the first "apothecary-sister" of this hospital.

An unusual plan was tried at Dijon, where the civil authorities had created a service for medical assistance to the poor in 1445. In 1528, this was expanded into the "Chamber of the Poor," management of which was entrusted to a physician and a surgeon. In 1551, an apothecary was added.

The Chamber decided, in 1643, to create a "Shop of Pharmacy" at the hospital and install sisters as apothecaries. It was originally intended that two master-apothecaries would appear thrice weekly to instruct the nuns. The former were also to prepare a book, in French, of all the preparations it would be necessary to make in the shop. On their part, the nuns were to manage the shop, and collect and prepare in season the herbs and the products made from them. The system worked quite well until 1652, when Sister Pierrette Courtois, in charge of the apothecary, refused to obey the administrators. Trouble continued until 1682, when the régimé of the nuns was abolished for about a year. The following year, the sisters were reinstalled. But things still went badly, for the apothecaries failed to visit the hospital regularly, and the nuns did not always do their work conscientiously. Finally, the sisters were given full control and the apothecaries only appeared occasionally to give instruction. Because the Chamber became convinced that the nuns were incompetent as buyers of good primary materials, it appointed in 1695 an apothecary to see to their instruction. Four years later, a city apothecary was elected to supply materials and inspect the pharmaceutical service of the hospital. In 1738, three books by Lemery were purchased for the hospital. They were his "Chimie," "Traité Universel des Drogues," and "Pharmacopee." Gradually, and partly due to their own bickerings, the apothecaries lost control over the hospital pharmacy.

Similar troubles prevailed at Lyons from 1656 to 1785.

The history of the Hôtel-Dieu de Pontoise is dealt with in great detail, particularly from 1629. The hospital was administered by the Augustine de Saint Nicolas sisters. A great deal of the material deals with the correspondence between the nuns and the widow Tranchepain. The business connection had begun in 1683, when the latter's husband, a Paris druggist, had established an account at the hospital. After his death, the widow carried on the business. Metinier, who became procuror about 1727, furnished a memorandum listing in detail the products supplied. A few of those mentioned are presented here:

". . . 2 ounces catheteric and specific onitment	03 L. 10s.
2 ounces white anodyne ointment	02 L. 00s.
11 ounces Balm of Fioraventy	22 L. 00s.
* * *	
Application at various times of catheteric spirit	02 L. 00s."

When mineral waters were needed, the sisters bought directly, as the waters of Abbey-du-Val and Passy.

Numerous other apothecaries who supplied the hospital pharmacy are listed. Most important of all was probably one Brechot, Pontoise apothecary, who furnished drugs from 1732 to 1745. Some of his memoranda are reproduced for the light they shed on the medicines of the time. A few excerpts from these are listed below:

". . . 5½ ounces syrup of violet
An opiate weighing 15 ounces composed of quinine, contrajerva, salt of Mars, of Riviera, of absinthe, of tamarind, prepared iron, and syrup of absinthe.

* * *

For Madame, 2 ounces catechu prepared with violet
3 purgative enemas

* * *

30 drops spirit of vitriol (2 times)
6 ounces syrup of violet
1 ounce laxative violet syrup

* * *

4 half-packages rhubarb in powder
2 ounces syrup of marshmallow
½ package confection of hyacinth

* * *

2 ounces sweet oil of almonds
Spirit of wine
6 boluses spermaceti, powdered gamboge, rhubarb, and sugar candy

* * *

Emulsified medicine
2 ounces honey of Narbonne
1½ packages crushed amber

* * *

Plaster for the teeth
For Madame, her opiate

* * *

1 package and 48 grains of native cinnabar
2 handsful veronica
10 ounces distilled water of black cherries

* * *

For Madame, 7 ounces syrup of maidenhair fern

* * *

For Madame Sainte-Scholastique, a citron
8 boluses of Kermes' crayfish eyes, and syrup of diacodion

* * *

8 1/2 ounces orange flower water

* * *

1 ounce of white poppy seeds

* * *

An opiate for Madame, divided in 12 doses, and composed of extracts of cerula campana, cress, chicory, absinthe, diaphoretic, gum ammoniac, galbanum, opoponax, sagapenum, and syrup of absinthe.

* * *

1 1/2 package salt of duobos (K_2SO_4?)
2 packages spirit of dulcified salt. . . . . ."

Incidentally, the author notes that the cost of these and other articles listed totaled over 115 livres. A balance of 40 livres was owed in December, 1743, which was not paid until January, 1745, ". . . the delay in payment being normal to that time."

CHAPTER III

Role of the Nuns in Convent Pharmacies

"It is necessary to believe that the sale of medicaments constituted an important source of revenue for the convents, inasmuch as the greater part was an entirely commercial traffic in remedies, which in principle should be distributed gratuitously to the poor."

The notable exceptions were the "Miramiones," or Daughters of Saint Geneviève. Their convent was a veritable clinic, and Mme. de Miramion, who supported the dispensary, paid out more than 1500 livres per year for the remedies used.

Various other orders and their activities are noted:

The Benedictine nuns at Moret were known for their sugars and syrups for whooping cough and affections of the breast. Those at Traisnel sold a famous lavender water, so popular that it brought an income of 7000 livres in 1737.

The Bernardines were the targets for the apothecaries' complaints at Bourges, in 1789. The latter claimed that all medicines were sold publicly, and refused to the poor for whom they were intended.

The Carmelites perhaps interest us the most because they had a pharmacopœia composed especially for their use. The author was Pierre Dufresnois. It appears from the preface that the book was prepared at the request of Mme. Seguier, Prioress at Pontoise at various times from 1624 to 1672. Two sentences selected from the preface indicate the pride of the writer: ". . . Indeed, Madame, I venture to say that there is nothing in all the extent of pharmacy which is not comprised in this little volume I send you. . . . it is, Madame, the passion I have had for you to learn all my secrets, and to confide to you all that experience, travels, and the capable people of my profession have come to learn regarding that which you wish to know, and that with which I have perfectly acquainted you. . . ." The work is divided into two parts, preceded by a section on weights and measures. The first section deals with the choice and preparation of the simple medicaments entering into various compounds. The second is a dispensatory of the most-used compositions, including numerous "particular secrets," both of medicine and cosmetics.

Apparently, other Carmelite houses trafficked in medicines. In some cases, the sister in charge had spent a short time at the Hôtel-Dieu in Paris, or elsewhere, to learn bleeding and pharmacy. From the records available, it appears that most of the remedies used were purgatives and calmatives.

The nuns of the abbey of Chaillot, of the Convent of Sainte-Perrine, were given the privilege of vending a balsamic syrup in 1728. The reported profits the first year were 3000 livres, and a prospectus was prepared which described the supposed properties and uses. (This is reproduced in its entirety.) It is interesting to note that none of the various distributors listed were apothecaries.

At La Maison de L'Enfant-Jésus, there was a remarkable apothecary: "Not alone by the medicaments found there, but also by the curiosities of natural history that one can admire there, by the laboratory furnished with apparatus and by the room for drying the balsamic herbs collected in the large garden of seven hectares which extends behind the buildings." The Hospitalieres de la Rue Mouffetard also had a well-equipped apothecary.

Various other groups are mentioned, many of whom made and distributed some remedy.

The religious community of Port-Royal de Paris had a medical personnel of sufficient importance to get considerable allotments of money. Among the drugs employed there, one finds cassia, scammony, senna, licorice, clove, pepper, ass milk, triticum, nutmeg, sweet almond oil, viper, cinchona and various mineral waters.

THE ROLE OF THE MONKS IN CONVENT PHARMACIES

The Augustines.—A letter of Guy Patin, written in 1660, testifies to the medical practice of one Brother Valérien, Augustine monk, who promised to cure the lawyer Pucelle. It was said that the Brother had two particular secrets either unknown to or ignored by the physicians. Valérien had gained some notoriety previously by the preparation of a water. The product was said to heal all sorts of maladies.

The Benedictines.—This order gained its greatest pharmaceutical fame through the "Onguent du Bec," first prepared by Dom Leclerc, and named after the abbey in which he worked. An elaborate prospectus is reproduced. This latter is divided into two parts, first describing the "virtues," and

then the mode of application in the various disorders. A few of the claims follow:

"... generally proper for the healing of all wounds."
"... works by transpiration. ..."
"It extracts all the wounds of foreign bodies... ordinarily in less than twenty-four hours, and without pain."
"... to heal all the ills which frequently come to the breasts of women. ..."
"It cures all sorts of fevers. ..."
"It brings happy accouchements to women in child labor."
"It returns the menses. ..."
"It extracts the humour of the gout."
"... the lives of many persons have been saved by this ointment."

In 1766, the *Ecclesiastic Journal* announced the distributors of the product for the benefit of the people of the provinces. The price was raised in 1768, due to the great demand.

The ointment was supposedly made of burgundy pitch, lard, yellow wax, naval pitch, rosin and powdered frankincense.

The Capuchins.—Numerous Capuchin groups prepared remedies.

Father Hilarion had a prescription "to dissipate the stone," made with white wine and celandine. He was also known for his diuretic infusion. Brother Joachim, of Paris, had a laxative syrup containing oil of tartar, spirit of vitriol, and polychresticum.

At Alençon, the Capuchins rendered great service in the epidemic of 1638. They had an "apothecary-Brother," who was a great botanist, and who painted some six hundred plants or flowers in natural colors. His studies were facilitated by a large monastery garden.

At Faubourg St. Jacques lived the famous Brother Ange, who distributed among other things "an opiate" and a "syrup mésenterique et épatique." His opiate cordial was made with preserved apricots, poppy flowers, sal ammoniac, sugar, etc. The product was used to purify the blood, for queasy stomach, etc. The ingredients were sometimes varied. Ange also distributed a cream for redness of the face (made with farina and distilled vinegar), a laxative "vegetable water" and an antimony preparation.

His reputation was great, and his income proportionate. Even the Dauphin brought him to court, but found no relief in his remedies.

Perhaps the most famous of the Capuchins were those at the Louvre. They will be discussed separately.

REFERENCES

(1) Tournier, J., "Le Clergé et la Pharmacie," Paris, Librairie Caffin (1938).
(2) ————, *J. pharm. chim.*, **28** (1938), 191.

Book Reviews

The Pharmacological Basis of Therapeutics, by LOUIS GOODMAN, M.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine, and ALFRED GILMAN, Ph.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine. 1383 pages, illustrated. The Macmillan Company, New York, 1941. Price $12.50.

This book, which is intended to serve both the medical student and the practitioner, presents a new approach to the study of pharmacology, one which aims at a correlation of basic physiological principles with pharmacodynamics and of pathological physiology of disease with the actions and uses of drugs. The scope of the text is sufficiently wide to serve the student throughout the medical course and subject matter is of such a nature that it should be of value to the practicing physician in refreshing his fundamental knowledge of pharmacology and in keeping abreast of the latest advances.

The subject matter is grouped into twenty-six sections covering all drugs of recognized value, including those recently introduced, as well as the latest information concerning the actions and uses of older drugs of established prescription writing. There are twenty-six illustrations, sixty-seven tables and rather extensive bibliographies at the end of each chapter. The volume is thoroughly indexed with entries for both drugs and diseases. Because of its scope and the arrangement of material, the book should be of value not only to the student and practitioner of medicine but also to the pharmacist, particularly as a reference work.—A. G. D.

University of California, Hospital Formulary, prepared by a Committee of the University of California, Medical Center Staff. v + 270 pages. University of California Press, Berkeley, California. Price $2.00.

This little volume is a handbook of helpful information, particularly with reference to drugs and chemicals and is intended primarily for the use of the staff and student body of the University of California Medical Center. Among the more important subjects with which it deals are prescription writing, vehicles and coloring agents, buffered and isotonic solutions, some of the commonly used trade-marked preparations, drugs for diagnostic purposes, endocrine preparations, vaccines, serums and antitoxins, the vitamins, parenteral fluids, therapeutic index and procedures for pediatrics, dental formulary drug list, x-ray examinations, laboratory and clinical procedures, treatment of burns and treatment of acute poisoning. The book is printed on thin paper, is of a size convenient to carry in the pocket and contains such a wide variety of information of use to the physician and clinical laboratory worker that it should be widely used.—A. G. D.

An Introduction to Crystal Chemistry, by R. C. EVANS. xi + 388 pages, 5¼ x 8⅛. 1939. Cambridge: At the University Press; New York: The Macmillan Co. Price, $4.50.

This volume is devoted to the study of crystal structure to chemical composition. The general principles of this relationship are presented and illustrated by classes of compounds. It is maintained that there is no essential difference between the forces binding the atoms in a molecule and the forces holding these atoms together in a solid. Four types of bonds are described: the metallic bond holding the atoms of a metal in a solid; the ionic or polar bond, as in a crystal of sodium chloride; the homopolar or coördinate bond, for example, the carbon atoms in the diamond; and a weak residual bond, which may be observed in the coherence of inert gases when condensed to solids at low temperatures. A chapter on the quantitative-lattice theory completes the first part of the book. The major portion of Part II deals with systematic crystal chemistry. A bibliography of essential references is appended.—A. G. D.

The Endocrine Glands, by MAX A. GOLDZIEHER. 6½ x 9¼ in. Illustrated with 271 figures, xvi + 916 pages. 1939. New York: D. Appleton-Century Co., Inc. Price, $10.00.

This book of 916 pages presents a review of the ductless glands based on experience in the field of endocrinology gained over a period of more than three decades. Whereas the whole field of endocrinology is covered, therapy is emphasized. Because of this fact, it should serve the pharmacist as a useful reference work on endocrine products. References to the literature are given throughout the text and the book is well illustrated.—A. G. D.

Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, 5th Edition, prepared by the Editorial Board, W. W. Skinner, Chairman, Committee on Editing Methods of Analysis, E. M. Bailey, Chairman, L. E. Warren, J. W. Sale, G. G. Frary, H. A. Lepper and Marian E. Lapp. Published by the Association of Official Agricultural Chemists, P. O. Box 540, Benjamin Franklin Station, Washington, D. C. Price $5.00.

The Association was founded September 9, 1884. Dr. Harvey W. Wiley was a charter member, and the only surviving charter member is Charles W. Dabney, retired. The first edition was a bulletin of 50 pages. The present volume has over 700 pages and is evidence of the growth of this important work. Forty-three chapters present the contents of the fifth edition, published in 1940. Sixty-one illustrations are helpful to the text; the Definitions of "Terms and Explanatory Notes" are further guides and helps in using the "Methods of Analysis." Those engaged in analytical work are familiar with this "Book of Methods" and find a great need for it. The continued growth of the handbook has taxed the efforts of the Editorial Committee to condense the material without detracting from the usefulness of the volume to the user.—E. G. E.

The Chemistry of Antigens and Antibodies, by PROFESSOR J. R. MARRACK of the London Hospital. 194 pages. His Majesty's Stationery Office, London, 1939. Price 3*s*. net.

This report is in reality a revised edition of an earlier report by the same name, which was published in 1934. The author has collected the more important results of recent experimental work on the chemistry of antigens and antibodies and has attempted to coördinate them into a consistent theory. The degree of success with which he has achieved this may be measured by the fact that the demand for copies of the first report were greater than could be filled.—A. G. D.

The Anaerobic Bacteria and Their Activities in Nature and Diseases, 2 vols., by ELIZABETH MCCOY and L. S. MCCLUNG xxiii + 295 pages; and xi + 602 pages. 8½ x 11. 1939. Berkeley, Calif.: University of California Press. Price, $10.00.

The two volumes of this publication constitute a complete bibliography of anaerobic bacteria from 1816 to 1938. Volume I is an author index, in which the authors are listed in chronological order and in which the titles of the articles are given. There is also a list of the journals cited. Volume II contains the subject index arranged according to the following outline: habitat, culture method, morphology, metabolism, products of metabolism, physiology, serological studies, disease relations, classification, etc. At the end of the book, there is a ten-page list of anaerobic bacteria.—A. G. D.

Introductory Essays on the History of Pharmacy, by JOHN J. CORCORAN. 175 pages, 8¼ x 10¾. "Mimeoprinted," 1940. Minneapolis, Minn.: Burgess Publ. Co. Price, $2.40.

This book is a survey of the profession of pharmacy in which its development up to and including the present is traced. It is illustrated with seventeen readings from pharmaceutical literature. The material for this book has been selected from the journals and from reprinted articles discussing various phases of pharmaceutical practices, such as the making of medicine, pharmacopœias, American pharmacy, pharmaceutical literature, pharmacy in other lands and pharmacy in relation to the social picture. Valuable references are given to guide the reader to further sources of historical information. There is an appendix of collateral readings and references tabulated under selected headings, also a trade and securities survey of the drug, medicine and cosmetic industry. Whereas the volume is intended primarily as a textbook for students in colleges of pharmacy, it is believed that practicing pharmacists will find much in it to interest them.—A. G. D.

Simple Experiment on Physico-Chemical Principles, by M. L. SCHROFF and G. P. SRIVASTAVA. 1st Edition. xiii + 292 pages. The Indian Pharmaceutical Association, Benares Hindu University, 1940. Price 8s. 6d.

This book, which is one of the Indian pharmaceutical series, is based on a course of experimental physical chemistry offered to the students of pharmaceutical chemistry at the Benares Hindu University during the last eight years. Experiments of theoretic importance but without any bearing on pharmacy have been omitted. Theoretical discussions have been simplified to make them be intelligible to students who have had no mathematics beyond the high school stage. An unusual feature of the book is the data sheets given after each experiment. Some idea of the scope of the book may be gained from the titles of the chapters, *viz.*: determination of molecular weight by the vapor density method, study of behavior of binary mixtures on distillation and their relation to vapor pressure; study of the vapor pressure relationship when a mixture of two immiscible liquids is subjected to distillation; viscosity; surface tension and interfacial tension; refractive index; polarimetry; colorimetry and nephelometry; spectroscopy; determination of molecular weight by the freezing point method; distribution or partition coefficient; the measurement of p_H solutions by the indicator method; determination of indicator constant of indicators; determination of K_{I_n} of Phenolphthalein; K_a of Boric Acid and K_a of Sodium Borate; solubility of partially miscible liquids; solubility of solids in liquids; adsorption; colloids; electro-analysis; measurement of electromotive force; measurement of the conductivity of electrolytes. There is an appendix describing the setting up of a thermostat and tables giving certain physical-chemical data.—A. G. D.

NOTICE TO PROSPECTIVE CONTRIBUTORS OF PAPERS

The 89th Annual Meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION will be held in Detroit, Michigan, during the week of August 17th.

Please send the Secretary of the Scientific Section, R. R. No. 16, Box 728-B, Indianapolis, Indiana, the title of the paper which you wish to present, together with an abstract and other information requested in this notice.

In order to facilitate the presentation of papers, the officers have decided to continue the special Subsection, to meet concurrently with the First Session of the Scientific Section. The program of the Subsection will be announced later.

Please note the following requirements of the Scientific Section:

1. The complete title and brief abstract, not to exceed 250 words, must be in the hands of the Secretary *not later than May 15th*, in time for enclosure in the published program. Please advise the Secretary whether you will present the paper in person, also *whether a lantern will be required for presentation*.

2. Ten minutes shall be allowed for the reading of the paper. If the paper is too lengthy to be read in detail in this space of time it should be presented in abstract.

3. In writing the paper the author should follow the procedure outlined in "Notice to Contributors" published in the Scientific Journal.

4. The by-laws provide that papers shall be presented in duplicate so that one copy will be available for publication, and the other copy for the use of the Committee on Ebert Prize. These copies should be mailed to the Secretary so as to arrive before July 15th or delivered to him at the Annual Meeting.

Our by-laws also require that before publication all papers must be passed by the Board of Review of Papers. Authors can assist the Board of Review of Papers if, when writing the original paper they eliminate all non-essential material, presenting the subject in short, concise form.

Your coöperation in submitting title and abstract promptly will greatly assist this office in preparing the program.

FRANCIS E. BIBBINS, *Secretary*,
Scientific Section,
R. R. No. 16, Box 728-B,
Indianapolis, Indiana